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Vol. 13, No. 4, October 1949

A METHOD OF IMPROVING FUNCTION OF THE BOWEL

J. ARNOLD BARGEN, M.D.,
Division of Medicine, Mayo Clinic, Rochester, Minnesota

Constipation, probably the commonest of physical complaints, may be caused by several factors, singly or combined: *1.* nervous fatigue and nervous tension; *2.* improper intake of fluid; *3.* improper dietary habits; *4.* failure to heed the call to stool; *5.* lack of exercise, and *6.* excessive use of laxatives.

It would seem logical that correction of constipation lies in the suitable adjustment of these factors.

Any diet for relief of constipation must supply material which has limited absorption in the small intestines and which adds bulk in the colon, i.e., fruits and vegetables. Daily fluid intake, from 2.5 to 3.5 liters, is highly important. Since many people find it difficult to eat enough dietary bulk, the trend recently has been toward hydrophilous colloids.

A search was made for such a colloid, for oral use, which has little or no effect in the stomach and small intestines. Methylcellulose, appropriately prepared as Cellothyl tablets, seems to answer these criteria.

A large number of patients received 4 tablets every 4 hours, with subsequent relief of constipation. These patients had no ordinary form of constipation; they had taken quantities, or as some said, "barrels of laxatives." In the following cases of obstinate constipation of long duration, a striking change for the better followed the use of this preparation, as part of a program of general medical care:

RESULTS OF TREATMENT

Case 1. Woman, age 57.—Obstinate constipation since early childhood. *After treatment:* Complete relief. She continued to pass normal, soft formed stools.

Case 2. Nun, age 69.—Obstinate constipation of lifelong duration. *After treatment:* In about a week . . . soft stools.

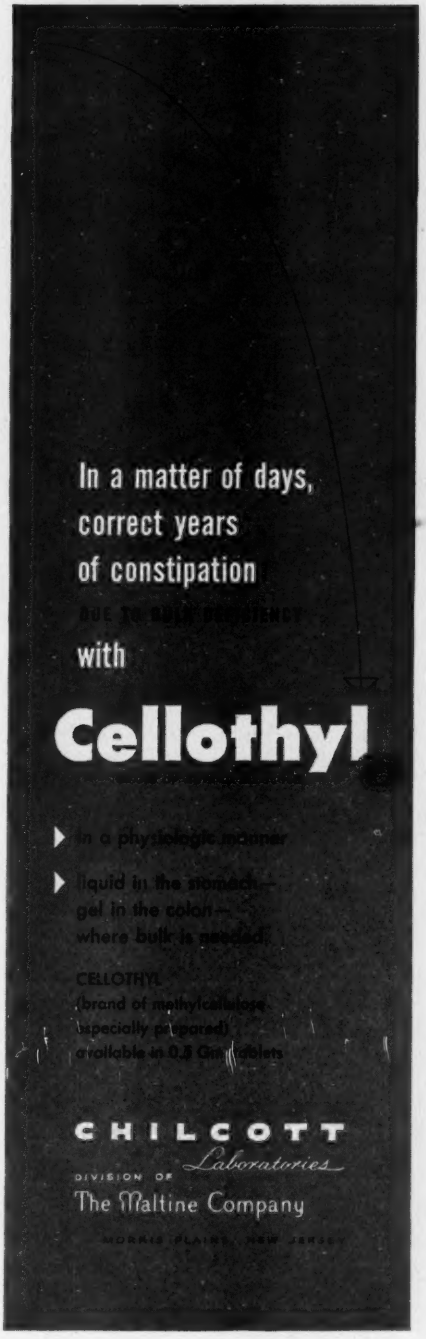
Case 3. Man, age 44.—Constipated many years; severe diabetes. *After treatment:* Normal stools at the end of one week.

Case 4. Woman, age 62.—Very difficult evacuation after carcinoma removal. *After treatment:* She passed her stools without discomfort.

Case 5. Woman, age 19.—Obstinate constipation; she had taken a laxative almost daily since early childhood. *After treatment:* At the end of two weeks she was passing stools daily.

COMMENT

Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared (Cellothyl). It represents a valuable addition to the well-ordered program of medical care.



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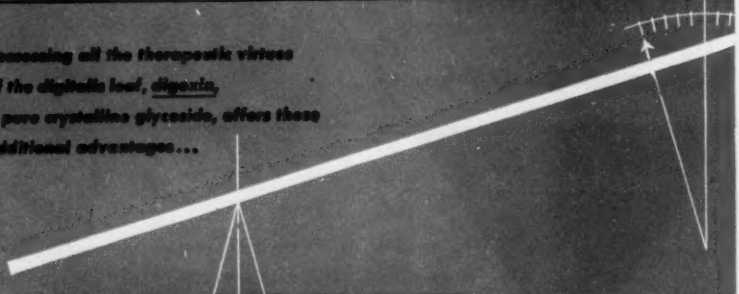

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EFFECTS OF CORTISONE ACETATE AND PITUITARY ACTH ON RHEUMATOID ARTHRITIS, RHEUMATIC FEVER AND CERTAIN OTHER CONDITIONS

A Study in Clinical Physiology

PHILIP S. HENCH, M.D.

EDWARD C. KENDALL, Ph.D.

CHARLES H. SLOCUMB, M.D.

AND

HOWARD F. POLLEY, M.D.

ROCHESTER, MINN.

PATIENTS with rheumatoid arthritis, acute rheumatic fever, certain other diseases with articular complications and certain nonrheumatic diseases have been improved markedly and promptly, but usually temporarily, by intramuscular injections of cortisone or ACTH. Cortisone is the hormone of the adrenal cortex previously known as compound E (17-hydroxy-11-dehydrocorticosterone). ACTH is the pituitary adrenal corticotropic hormone which stimulates responsive adrenal glands to produce cortisone or a cortisone-like steroid such as compound F.

Our preliminary results have been reported.[1] Herein are presented further experiences with these hormones. Because they are still scarce

From the Division of Medicine (Drs. Hench, Slocumb and Polley) and the Division of Biochemistry (Dr. Kendall), Mayo Clinic.

1. (*a*) Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181 (April 13) 1949; Ann. Rheumat. Dis. **8**:97 (June) 1949. (*b*) Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C.: The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:277 (May 25) 1949. (*c*) Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex, Cortisone (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis and Acute Rheumatic Fever, Tr. A. Am. Physicians **62**:64, 1949; (*d*) The Effects of the Adrenal Cortical Hormone (17-Hydroxy-11-Dehydrocorticosterone: Cortisone) and of Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatoid Arthritis and Rheumatic Fever, in the Proceedings of the Seventh International Congress on Rheumatic Diseases, New York, May 30-June 3, 1949, to be published.

and because our experience with them is still limited, this report, like our preceding one, is presented as a study in clinical physiology and not as a report on clinical therapeutics.

STUDIES WHICH LED TO OUR USE OF THESE HORMONES

In 1925 the weakness, fatigue and low blood pressure common among patients with rheumatoid arthritis (which we then called "chronic infectious arthritis") suggested to one of us that, in connection with or in addition to a supposed factor of infection, secondary metabolic changes were present and that the adrenal glands might somehow be involved in this disease. But the examination, in 1925, of the adrenal glands of 2 patients with rheumatoid arthritis who died lent no support to the vague suspicion regarding an adrenal factor, and the notion was laid aside for a while.[2]

In 1929 studies were begun on the amelioration of rheumatoid arthritis by jaundice.[3] It was concluded that, contrary to the general opinion, rheumatoid arthritis was potentially reversible and was "not necessarily a relentlessly progressive uncontrollable disease for which no really satisfactory and rapid method of control need ever be expected." The dominant feature of jaundice suggested that the unknown ameliorating agent, which we named "antirheumatic substance X," was a hepatic or biliary constituent. Hepatic substances and procedures related to jaundice were applied to rheumatoid arthritis without success.

Between 1931 and 1938 the beneficial effect of pregnancy on rheumatoid arthritis was studied.[4] As a result, our ideas as to the probable nature of substance X changed radically. Was the agent responsible for the relief of rheumatoid arthritis by pregnancy the same as, or closely related to, that operating during jaundice? If so, it could be neither bilirubin nor a unisexual (female) hormone, because jaundiced rheumatoid men obtained the same relief as pregnant rheumatoid women without jaundice. It was then conjectured that the hypothetic substance X was not a disintegration product from damaged liver but probably was a biologic compound specific in nature and function, one which was normal to the human

2. (*a*) Hench, P. S.: The Protean Manifestations of Chronic Infectious Arthritis (with a Note on Treatment), M. Clin. North America **8**:1295 (Jan.) 1925; (*b*) The Systemic Nature of Chronic Infectious Arthritis, Atlantic Monthly **28**:425 (April) 1925.

3. (*a*) Hench, P. S.: Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis and Sciatic Pain, Proc. Staff Meet., Mayo Clin. **8**:430 (July 12) 1933; (*b*) The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, Ann. Int. Med. **7**:1278 (April) 1934; (*c*) Effect of Jaundice on Chronic Infectious (Atrophic) Arthritis and on Primary Fibrositis: Further Observations; Attempts to Reproduce the Phenomenon, Arch. Int. Med. **61**:451 (March) 1938; (*d*) The Advantages of Hepatic Injury and Jaundice in Certain Conditions, Notably the Rheumatic Diseases, M. Clin. North America **24**:1209 (July) 1940; (*e*) Effect of Jaundice on Chronic Infectious Arthritis and Primary Fibrositis, J. A. M. A. **109**:1481 (Oct. 30) 1937; (*f*) Effect of Spontaneous Jaundice on Rheumatoid (Atrophic) Arthritis, Brit. M. J. **2**:394 (Aug. 20) 1938.

4. Hench, P. S.: The Ameliorating Effect of Pregnancy on Chronic Atrophic (Infectious, Rheumatoid) Arthritis, Fibrositis and Intermittent Hydrarthrosis, Proc. Staff Meet., Mayo Clin. **13**:161 (March 16) 1938.

organism and of which, perhaps, the arthritic patient did not have enough.[5] Since pregnancy alters the concentration of hormones, we began to suspect that substance X might be a bisexual steroid hormone. Among substances which came under our consideration in 1938 we listed whole adrenal cortex extract, then called "cortin," but we did not use it until later.

Prior to 1938 we regarded substance X as only antirheumatic. Then it was noted that pregnancy or jaundice sometimes relieved temporarily such nonrheumatic conditions as hay fever, asthma, sensitivity to egg, migraine and psoriasis. Hence we concluded that this phenomenon of relief was not disease specific—that is, specific for rheumatoid arthritis alone—but was group specific. This lent impetus to our search, because we now suspected that if substance X could be identified it would be useful against a number of diseases.

In an attempt to identify substance X many conferences were held by Hench and Kendall. Many possibilities were discussed, among them the idea of an adrenal factor in rheumatoid arthritis. After such a discussion in January 1941, we decided to try compound E whenever it might become available. A note to that effect was made, but none was available for use on human beings.

After five years of work attempting to extract adrenal cortex hormones, Mason, Myers and Kendall isolated compound E in 1935.[6] But only a small amount of natural compound E had been extracted by January 1941. Synthesis had not yet been attempted.

In lieu of compound E we gave Kendall's adrenal cortex extract, "cortin," to 3 patients with rheumatoid arthritis. The first patient, a girl aged 15 years, was admitted to the Mayo Clinic July 16, 1941. Her polyarthritis was of three years' duration. After she received the extract intravenously (10 cc. twice a day) for four days, certain joints were less swollen and painful; others were still swollen. Similar doses were given for four more days, during which time the earlier improvement diminished. The sedimentation rate fell slightly, from 74 to 60 mm. in one hour. Two other patients so treated also obtained unimpressive results.

With no compound E or other likely adrenal product available to us, we then produced jaundice with lactophenin in arthritic volunteers. Temporary remissions were induced, but we could not identify the responsible agent.[7]

Meanwhile a prodigious cooperative effort to produce compound E in some quantity was being made by Kendall and his associates of the clinic and by research chemists of Merck & Co., Inc., in particular, Dr. L. H. Sarett.[8] But enough was

5. (*a*) Hench.[3] (*b*) Hench, P. S.: The Potential Reversibility of Rheumatoid Arthritis, Ann. Rheumat. Dis. **8**:90 (June) 1949; Proc. Staff Meet., Mayo Clin. **24**:167 (March 30) 1949.

6. Mason, H. L.; Myers, C. S., and Kendall, E. C.: (*a*) The Chemistry of Crystalline Substances Isolated from the Suprarenal Gland, J. Biol. Chem. **114**: 613 (July) 1936; (*b*) Chemical Studies of the Suprarenal Cortex: II. The Identification of a Substance Which Possesses the Qualitative Action of Cortin: Its Conversion into a Diketone Closely Related to Androstenedione, ibid. **116**:267 (Nov.) 1936. (*c*) Mason, H. L.; Hoehn, W. M., and Kendall, E. C.: Chemical Studies of the Suprarenal Cortex: IV. Structures of Compounds C, D, E, F and G., ibid. **124**:459 (July) 1938.

7. (*a*) Hanssen, P.: The Effect of Lactophenin-Icterus on Chronic Infectious Arthritis, Acta med. Scandinav. **109**:494, 1942. (*b*) Hench.[6b]

8. Sarett, L. H.: (*a*) Partial Synthesis of Pregnene-4-Triol-17 (β), 20 (β)-21-Dione-3, 11 and Pregnene-4-Diol-17 (β), 21-Trione-3, 11, 20 Monoacetate, J. Biol. Chem. **162**:601 (March) 1946; (*b*) A New Method for the Preparation of 17 (α)-Hydroxy-20-Ketopregnanes, J. Am. Chem. Soc. **70**:1454 (April) 1948.

not available for clinical testing in human patients until May 1948. During the next two or three months small amounts were given to a few patients with Addison's disease at three medical centers. Results were satisfactory.[9] But if its use was limited only to the treatment of Addison's disease there would be a small field of usefulness.

In August 1948, we tried to relieve a woman badly crippled with rheumatoid arthritis by means of jaundice induced by lactophenin, but no jaundice developed. We then decided to try compound E if it was available. Our earlier conjecture that substance X might be an adrenal hormone had meanwhile become strengthened by our observations that rheumatoid arthritis was often temporarily relieved by seemingly diverse agents (foreign protein reactions, starvation, various surgical operations and even anesthesia without surgery), some of which were capable of stimulating the adrenal cortexes.[5b]

A letter requesting sufficient compound E for 1 patient was sent to Merck & Co., Inc., Sept. 4, 1948. The letter concluded: "We know that there is a potentially provokable mechanism (for the reversibility of rheumatoid arthritis) which is activated by pregnancy and jaundice very rapidly, by jaundice for example within 3 days. . . . Therefore if any adrenal compound is of real significance in rheumatoid arthritis we would expect to see some results within a very few days." A small supply of compound E was received and first administered to the patient on Sept. 21, 1948.

SELECTION OF PATIENTS AND METHODS OF STUDY

Number of Patients Studied.—Since Sept. 21, 1948, we have given compound E (which we later renamed cortisone) or compound E acetate to 21 patients with rheumatoid arthritis. The pituitary hormone ACTH was given to 6 rheumatoid patients: to 4 who also received cortisone and to 2 who did not receive cortisone. Thus a total of 23 rheumatoid patients received either cortisone or ACTH or both. Nine of these patients also received one or more of 12 related substances,[10] the results of which will be reported elsewhere.

Selection of Patients.—To demonstrate effects of cortisone, ACTH or related substances, we chose patients so disabled that whatever

9. (*a*) Perera, G. A.; Pines, K. L.; Hamilton, H. B., and Vislocky, K.: Clinical and Metabolic Study of 11-Dehydro-17-Hydroxy-Corticosterone Acetate (Kendall Compound E) in Hypertension, Addison's Disease and Diabetes Mellitus, Am. J. Med. **7**:56 (July) 1949. (*b*) Sprague, R. G.; Kepler, E. J.; Keating, F. R., Jr., and Power, M. H.: Coexisting Addison's Disease and Diabetes Mellitus: Comparative Effects of Compound E (17-Hydroxy-11-Dehydro-Corticosterone) and Allied Substances in Three Cases, abstracted, J. Clin. Investigation **26**:1198 (Nov.) 1947.

10. The various preparations used were supplied by the following persons: cortisone and compound A (11-dehydrocorticosterone) by Drs. Randolph Major, Vice President, and James M. Carlisle, Medical Director, Merck & Co., Inc.; ACTH, by Dr. John R. Mote, Medical Director, The Armour Laboratories; compound F (17-hydroxycorticosterone), by Drs. E. Gifford Upjohn and H. F. Hailman, The Upjohn Co.

improvement resulted would be unmistakably obvious but excluded those with irreversible, permanent residual deformities. All the patients had chronic disabling polyarticular rheumatoid arthritis graded as moderately severe, severe or very severe.

In table 1 are certain data concerning the 23 patients, of whom 11 were female and 12 were male. Ages varied from 17 to 64 years. The duration of chronic arthritis was 3 and 4.5 months in 2 patients who had previously had episodic rheumatoid arthritis, 5 months each in 2 patients already greatly disabled despite the short duration of their illness, and 10 months to 11 years in the remaining 19 patients. Most of the patients walked with difficulty and required help to get into or out of bed or up from a chair. Fifteen of the 23 patients had flexion contractures of knees, elbows or shoulders. One patient had been using crutches intermittently for seven months and constantly for two months; another had been using, for eleven weeks, a wheel chair except for a few halting steps. Several patients were bedridden by acute episodes. Sedimentation rates were elevated in all cases, markedly in most.

Additional Remedies.—Use of whatever remedies were being employed was stopped before the preparations under study were administered. While cortisone or ACTH was being given, no supplements of any kind were used in the early cases. But later, after the effectiveness of these hormones was established, we occasionally reduced the doses of cortisone to inadequate or ineffective amounts, which were then supplemented by acetylsalicylic acid in 2 cases, vitamin C in 3 cases and focal removal in 1 case. This was done to see whether these procedures would enhance the effectiveness of cortisone.

Evaluation of Results.—Many biochemical tests and motion pictures were made of all patients before, during and after the use of cortisone or ACTH. The motion pictures showed the patient rising as best he could from a sitting position in an armless chair, walking, climbing over a testing stairs, 3 steps up and 3 steps down, and then sitting down; they also showed his visual responses to pressure applied to representative joints. Special charts were used to record the changing condition of each affected joint: articular redness, swelling, tenderness, limitation of motion and the patient's estimate of his pain at rest, stiffness and pain on voluntary and on forced motion of affected joints. The scale of grading was grade 1, mild; grade 2, moderate; grade 3, marked, and grade 4, very marked. To evaluate tenderness firm pressure was used: tenderness grade 1— represented barely perceptible tenderness on firm pressure; grade 1, mild but definite tenderness; grade 2 moderate tenderness (rather uncomfortable but still tolerable). Tenderness grade 2+ bordered on the limits of tolerance and pressure on such joints made patients wince, express vocal reactions or instinctively withdraw the examined part. Tenderness grade 3 was marked; on joints considered to be "tender, grade 3," patients reluctantly allowed only one pressure at any one examination. This degree of tenderness is characteristic of acute rheumatoid arthritis or acute flare-up

of chronic arthritis. Tenderness grade 4 is not characteristic of rheumatoid arthritis, even with acute activity, but is characteristic of severe acute gouty arthritis or acute rheumatic fever.

After our chartings we often said to the patient: "We now have our idea of the condition of your joints. What is your own idea?" The patient often summed up matters by stating simply, "I've lost half of my rheumatism" or 80 or 90 per cent, which usually meant subjective relief and was not an over-all appraisal, including objective data. A patient might be subjectively "100 per cent relieved," but if firm pressure revealed residual tenderness our estimate of the over-all relief was not 100 per cent but lower. Although such over-all summations involved personal interpretations, we found them useful, and we believe that such "total scores" were rather accurate, as they involved also consideration of laboratory data and motion pictures.

USE OF CORTISONE IN RHEUMATOID ARTHRITIS

Preparations Used.—One of the important decisions of this investigation concerned the method of giving of compound E. We were guided by the fact that compound E was absorbed more rapidly than was the acetate of this compound [11] and by the desire to simulate as closely as possible the continued liberation of the hormone from the adrenal gland. To accomplish this, a large dose of finely ground crystals suspended in isotonic sodium chloride solution was injected intramuscularly. At first, compound E was finely ground in a mortar and a suspension of 25 mg. per cubic centimeter of solution was prepared. Later, after much time and effort, a more satisfactory suspension of the same weight of material was prepared in a miniature-sized ball mill composed of an Erlenmeyer flask and glass beads.[12] A wetting agent, tween 80® (the polyoxyalkylene ether of partial lauric acid esters), was found to be helpful. Ninety per cent of the particles were less than 10 microns and 30 per cent were less than 5 microns. Eventually it was found that the acetate of compound E when ground under the same conditions was absorbed satisfactorily.

Compound E was used between September 1948 and Jan. 19, 1949. Since that time only compound E acetate has been given. Since April 1949 Merck & Co., Inc., has furnished compound E acetate prepared ready for use.

Toxicity of Cortisone Acetate.—In general, no reactions from toxicity have been encountered. Rarely a febrile reaction resulted from a given injection, perhaps due to pyrogens in a particular bottle. Such a

11. Sprague, R. G.; Power, M. H.; Mason, H. L., and Cluxton, H. E.: Metabolic Effects of Synthetic Compound, abstracted, J. Clin. Investigation **28**:812 (July) 1949.

12. Kendall, E. C.: Some Observations on the Hormone of the Adrenal Cortex Designated Compound E, Proc. Staff Meet., Mayo Clin. **24**:298 (May 25) 1949.

sample was returned for analysis and repurification, and another bottled preparation was used. Most preparations caused no significant pain when injected intramuscularly.

Controls.—To provide controls, intragluteal injections (100 mg. daily) of an inert substance, a suspension of cholesterol indistinguishable in appearance from cortisone, were given to many of our patients, sometimes for a few days before, sometimes for a few days after, the administration of cortisone. The times when the control solution and the adrenal hormone were interchanged were always unknown to the patients and were, for five weeks, unknown to the three clinical authors who were evaluating results. When the use of cholesterol preceded that of cortisone, no outstanding clinical or biochemical alterations occurred until the control solution was replaced by cortisone. Likewise, when cortisone was replaced by cholesterol, symptoms generally returned within a few days and sedimentation rates rose.

General Plan of Dosage.—Of cortisone, 100 mg. generally was administered intragluteally once daily or 50 mg. was injected twice a day. On special occasions 150 or 200 mg. was given daily for a short time. Of cortisone acetate, 300 mg. was usually given the first day (150 mg. into each buttock) and thereafter 100 mg. daily. A single daily dose of 100 mg. appeared generally to be as effective as 50 mg. twice a day. One hundred milligrams of cortisone acetate is the chemical equivalent of about 89 mg. of cortisone.

In our cases (all severe), daily doses of 75 mg. were usually incompletely effective; smaller doses, of 25 or 50 mg., daily were inadequate or totally ineffective.

Early Concepts Regarding Dosage and Length of Administration.—Four of the first 5 patients received cortisone more or less continually for several months, and most of the later patients received one or more shorter courses of cortisone.

In planning the daily dose and length of administration of cortisone in a given case we had to rely chiefly on the patient's clinical response, the effect of cortisone on symptoms and sedimentation rates. It was soon noted that symptoms were largely controlled by doses of 100 mg. daily but were not controlled by much smaller doses. Hence we reverted to the larger doses of 100 mg. daily and kept the earlier patients on that dose more or less continually for relatively long periods to see whether the disease could be thus controlled.

The 4 early patients who were studied in the fall and winter of 1948 did well while receiving cortisone more or less constantly for several weeks. Then certain signs of hypercortisonism slowly appeared. In 3 cases (cases 2, 3 and 5) the signs and symptoms were mild, but

in case 1, in which cortisone or cortisone acetate was administered continually for six months, depression and other symptoms slowly appeared.

Early in the spring of 1949 we altered our general plan of administration of cortisone. (Hereafter the term "cortisone" will be used in a generic sense and will refer to cortisone acetate unless otherwise specified.) Thereafter we usually gave two or more fairly short courses of cortisone with some days or weeks between courses. This was done (1) to avert or minimize the development of hypercortisonism, (2) to determine how far the arthritis would relapse after a short course of cortisone and (3) to determine whether relapses would respond to further cortisone therapy.

The length of courses varied because of many factors (table). Courses were often stopped because our supply of cortisone was exhausted. Sometimes when sedimentation rates quickly became normal but minor symptoms persisted, treatment was continued to determine whether symptoms could be completely eliminated. Sometimes symptoms were quickly controlled by cortisone but sedimentation rates decreased tardily; the use of cortisone was continued in an attempt to restore rates also to normal.

USE OF ACTH IN RHEUMATOID ARTHRITIS

Development of ACTH.—Early data relating the anterior pituitary lobe to the adrenal cortex and demonstrating an effect on the latter of crude anterior pituitary extract [13] were extended in 1933 by Collip and associates,[14] who isolated a relatively purified fraction of the adrenocorticotropic principle. Further purification was accomplished in 1942 and 1943 by Li, Simpson and Evans [15] and by Sayers, White and Long.[16] Adrenocorticotropin was identified as a protein with a molecular weight of about 22,000. Because of the scarcity of material between 1943 and 1948, only a few clinical studies were made on a normal sub-

13. (*a*) Evans, H. M.: The Function of the Anterior Hypophysis, in Harvey Lectures, 1923-1924, p. 212. (*b*) Smith, P. E.: The Disabilities Caused by Hypophysectomy and Their Repair: The Tuberal (Hypothalamic) Syndrome in the Rat, J. A. M. A. **88**:158 (Jan. 15) 1927; (*c*) Hypophysectomy and a Replacement Therapy in the Rat, Am. J. Anat. **45**:205 (March) 1930.

14. Collip, J. B.; Anderson, Evelyn M., and Thomson, D. L.: The Adrenotropic Hormone of the Anterior Pituitary Lobe, Lancet **2**:347 (Aug. 12) 1933.

15. (*a*) Li, C. H.; Simpson, M. E., and Evans, H. M.: Isolation of Adrenocorticotropic Hormone from Sheep Pituitaries, Science **96**:450 (Nov. 13) 1942. (*b*) Li, C. H.; Evans, H. M., and Simpson, M. E.: Adrenocorticotropic Hormone, J. Biol. Chem. **149**:413 (Aug.) 1943.

16. (*a*) Sayers, G.; White, A., and Long, C. N. H.: Preparation of Pituitary Adrenotropic Hormone, Proc. Soc. Exper. Biol. & Med. **52**:199 (March) 1943; (*b*) Preparation and Properties of Pituitary Adrenotropic Hormone, J. Biol. Chem. **149**:425 (Aug.) 1943.

Effects of Cortisone, ACTH, Compound A and Compound F on 23 Patients with Rheumatoid Arthritis

Case	Age * Yr.	Sex	Chronic Arthritis: Duration	Chronic Arthritis: Severity and Location †	Substances Given	Length of Administration, Days	Total Dosage, Gm.	Average Daily Dose, Mg.	Improvement
1	29	F	4 yr.	Severe R. A.	Cortisone or cortisone acetate	187	17.075	91	Marked
2	41	M	5 yr.‡	Severe R. A.; R. S.	1st course: cortisone	75	7.5	100	Marked
					2d course: cortisone or cortisone acetate	140	14.1	101	Marked
3	64	M	5 yr.‡	Severe R. A.	1st course: cortisone	60	6.0	100	Marked
					2d course: cortisone or cortisone acetate	85	8.5	100	Marked
					Compound A	9	0.9	100	No effect
					3d course: cortisone acetate	73	7.3	100	Marked
4	41	M	2 yr.‡	Moderately severe R. A.	1st course: cortisone	12	1.2	100	Marked
					2d course: cortisone or cortisone acetate	36 §	3.88	99	Marked
					3d course: cortisone acetate	61 ‖	6.6	98	Marked
5	34	M	4½ mo.‡	Very severe R. A.; R. S.	Cortisone or cortisone acetate	133	11.125	84	Very marked
6	49	F	3 yr.	Severe R. A.	Compound A	7	0.7	100	None
					1st course: cortisone	10	1.0	100	Marked
					ACTH	12	1.2	100	Marked
					Compound F	12	0.9	75	Moderate
					2d course: cortisone acetate	30	4.2	140	Marked
7	53	F	2 yr.	Moderately severe R. A.	Cortisone	25	2.5	100	Very marked
8	62	M	3 mo.‡	Severe R. A.	1st course: cortisone acetate	9	1.1	122	Very marked
					2d course: cortisone acetate	42	1.33	32	Mild
9	44	F	2 yr.	Severe R. A.	Cortisone	25	2.15	86	Very marked
10	49	M	5 mo.	Moderately severe R. A.	1st course: cortisone	61	9.25	152	Very marked
					2d course: cortisone acetate	40	6.1	153	Very marked
11	40	F	5⅝ yr.	Moderately severe R. A.	1st course: cortisone acetate	8	1.0	125	Very marked
					ACTH	12	1.26	105	Very marked
					2d course: cortisone acetate	18	3.6	200	Very marked
12	43	F	10 mo.	Moderately severe R. A.	1st course: cortisone acetate	57	5.9	104	Very marked
					2d course: cortisone acetate	57	5.7	100	Marked
13	31	F	5 yr.	Moderately severe R. A.	Cortisone acetate	29	3.7	128	Very marked
					Compound A	14	1.4	100	None
14	45	F	5 yr.	Moderately severe R. A.	ACTH	12	1.2	100	Very marked
					1st course: cortisone acetate	30	4.2	140	Marked
					2d course: cortisone acetate	18	3.6	200	Marked
					3d course: cortisone acetate	18	3.6	200	Marked
15	29	M	3 yr.	Severe R. A.	Cortisone acetate	64	8.25	129	Very marked
					ACTH	31	2.975	96	Very marked
16	49	M	10 mo.	Very severe R. A.	Cortisone acetate	161	18.85	117	Moderate
17	23	M	6½ yr.	Severe R. A.; R. S.	ACTH	11	0.77	70	Marked
18	38	M	6 yr.	Very severe R. A.; R. S.	ACTH	87	9.665	111	Very marked
19	30	M	11 yr.	Severe R. S.	Cortisone acetate	66	6.8	103	Marked
20	55	F	3 yr.	Moderately severe R. A.	Cortisone acetate	22	2.4	109	Very marked
21	30	F	5 yr.	Severe R. A.	Cortisone acetate	56	5.6	100	Very marked
22	22	M	3 yr.‡	Severe R. A.; R. S.	Cortisone acetate	32	3.2	100	Very marked
23	17	F	5 mo.	Very severe R. A.	1st course: cortisone acetate	38	4.0	105	Marked
					2d course: cortisone acetate	20	2.0	100	Very marked
					3d course: cortisone acetate	22	3.2	... ¶	Marked

* Some patients had a birthday in the hospital; the age given here is generally that of the patient when the first of the test substances was given and may or may not have been the patient's age on admission.

† R. A. means rheumatoid arthritis of peripheral joints; R. S. means rheumatoid arthritis of spine.

‡ These patients had episodic rheumatic symptoms before their disease became chronic.

§ Cortisone was given on thirty-six out of thirty-nine consecutive days; the average daily dose was calculated on a basis of thirty-nine days.

‖ Cortisone was given on sixty-one out of seventy-one consecutive days; the average daily dose was calculated on a basis of seventy-one days.

¶ During this "interrupted course" cortisone acetate was given interruptedly, for periods of two to seven days, with intervals of three to seven days between. Cortisone was given on twenty-two out of fifty-six consecutive days (Dec. 8, 1949 to Feb. 1, 1950).

ject and on patients with Addison's disease and other conditions.[17] Its effect on rheumatoid arthritis and related conditions was not suspected by the workers. The preparation used was that made by The Armour Laboratories from pituitary glands of hogs. Some commercial preparations have been clinically impotent or relatively so.

In 1948 Li [18] reported that the ACTH protein molecule could be broken down by pepsin digestion into a mixture of smaller units, a peptide fragment of low molecular weight, which retains the adrenal-stimulating properties of ACTH protein.

Rationale for the Use of ACTH in Rheumatoid Arthritis.—When we noted, in September 1948, the effect of cortisone on rheumatoid arthritis, it seemed logical to determine as soon as possible the effect of ACTH also, since ACTH stimulates responsive adrenal glands to produce cortisone or the cortisone-like substance, compound F. But we were unable to use ACTH until Feb. 8, 1949 (case 14). Before giving it, we were not certain what our results would be. If the adrenal glands of rheumatoid patients were producing, not cortisone, but an altered product related to the causation of the disease, stimulation of such adrenal glands might increase, rather than decrease, articular symptoms. A prompt answer was obtained when we observed that ACTH produced essentially the same antirheumatic effect as did cortisone.

Preparation Used.—We have used ACTH given to us through arrangements with Dr. John R. Mote, Director of Medical Research, The Armour Laboratories. The potency of different lots varied somewhat. Before use, the material is dissolved in saline solution. A preparation suspended in oil proved unsatisfactory.

Toxicity.—Current preparations of ACTH contain small but important amounts of "impurities," consisting mostly of posterior pituitary substance. Different lots contained from about 0.4 to 3.3 units of alpha hypophamine (oxytocin) per vial and about 0.5 to 5 units of

17. (*a*) Browne, J. S. L.: The Effect of Corticotropin on the Excretion of Cortin-like Substances and 17-Ketosteroids, Tr. Fourth Conf. Metabolic Aspects of Convalescence 1943, pp. 88-94. (*b*) Browne, J. S. L.; McAlpine, H. T., and Hoffman, M. M.: Metabolic Effects Produced by the Administration of Large Doses of Adrenocorticotrophic Hormone to Normal Humans, Tr. Seventeenth Conf. Metabolic Aspects of Convalescence, 1948, pp. 148-158. (*c*) Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. **8**:15 (Jan.) 1948. (*d*) Mason, H. L.; Power, M. H.; Rynearson, E. H.; Ciaramelli, L. C.; Li, C. H., and Evans, H. M.: Results of Administration of Anterior Pituitary Adrenocorticotropic Hormone to a Normal Human Subject, ibid. **8**:1 (Jan.) 1948.

18. Li, C. H.: Biochemistry of Adrenocorticotropic Hormone: A Review, Tr. Seventeenth Conf. Metabolic Aspects of Convalescence, 1948, pp. 114-138.

pressor substance per vial. We have observed no serious toxic reactions to ACTH in these rheumatoid patients.

General Plan of Dosage.—When we began the use of ACTH, we decided to administer intragluteally 100 mg. daily, since that was the usual total daily dose which other investigators at this clinic had given to a normal patient.[17d] Since then we generally have given daily 100 mg., occasionally 45 to 140 mg. Since ACTH is rapidly utilized by the body, the total daily dose must be given in divided doses. In our "severe" cases best results were obtained when injections were given every six or eight hours. The first 2 patients to receive ACTH (cases 14 and 6) did well when receiving 25 mg. at 8 a. m., 25 mg. at 4 p. m. and 50 mg. at 10 p. m.

Length of Administration.—Data regarding the 6 patients who received ACTH are given in the table. The hormone was given daily for eleven days in case 17, for twelve days each in 3 cases (6, 11 and 14), for thirty-one days in case 15 and for eighty-seven days in case 18.

ARRANGEMENT OF REPORTS OF CASES

Both of the hormones produced marked antirheumatic and certain other desirable effects. But when given long enough or in large enough doses, either was found to be capable of producing undesirable effects (that is, undesirable for rheumatoid patients), which for purposes of this report will be called "side effects," althought they, like the desirable results, are true physiologic effects.

To bring out the relationship of dosage and length of administration to the production of antirheumatic effects and side effects the cases will be reported, not in chronologic and numerical sequence, but in groups as follows: In group 1 the patients obtained marked antirheumatic effects with no or minimal side effects; in group 2, marked antirheumatic effects with mild side effects; in group 3, marked antirheumatic effects with moderate side effects, and in group 4, moderate or marked antirheumatic effects with marked side effects. Within each group the cases are arranged according to the total length of administration of cortisone and/or ACTH.

GROUP 1: MARKED ANTIRHEUMATIC EFFECT WITH NO OR MINIMAL SIDE EFFECTS

CASE 20.—*Moderately severe rheumatoid arthritis; very marked response to cortisone acetate*

A woman, 55 years old, began to have progressive polyarthritis in April 1946. In January 1948 her hands were so bad that she quit work as a telephone operator. Chrysotherapy was ineffective. She was admitted to the hospital June 17, 1949. Her appetite was poor. She was so stiff in the morning that she had to "drag

herself out of bed." Acetylsalicylic acid was withheld; pain and stiffness increased considerably. It took her five minutes to maneuver out of bed and two hours before she could comb her hair. It was difficult for her to wash her face or rise from the toilet. Many joints were swollen, tender and painful on forced motion. Roentgenograms revealed destructive changes in the wrists and hands.

Use of Cortisone Acetate.—This was given for twenty-two days (June 20 through July 11),[19] 300 mg. the first day and then 100 mg. daily (fig. 1). Nine hours after the first dose she noted less pain. Tenderness in the right wrist, which had been grade 2+, was now only slight, grade 1. That night she slept soundly. The next day she rose easily from bed and was able to comb her hair at once. "I haven't felt like this for two years. I feel like I did before I had arthritis, as if a great weight had been lifted from me." That night she was stimulated and had insomnia but no painful stiffness. After two days of use of

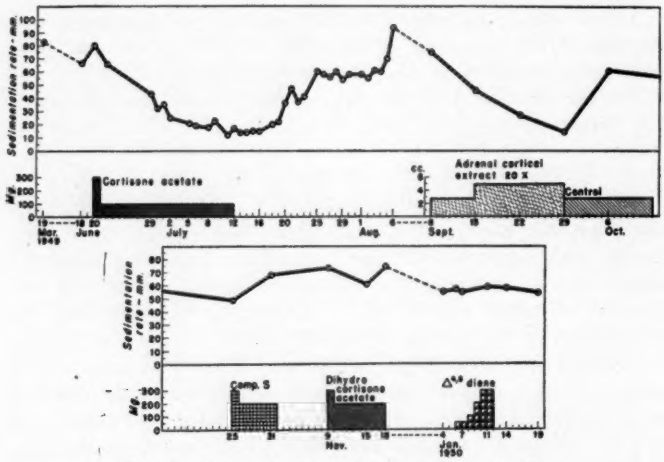

Fig. 1.—Curve of sedimentation rate in case 20.

cortisone, her joints were markedly improved. Within the next ten days, she lost practically all symptoms and swelling of joints. She was ravenous and ate between meals. There was a marked sense of well-being. After twenty-two days of cortisone her subjective symptoms had disappeared except for slight tightness of a shoulder. Except for slight swelling of a wrist, articular swellings had disappeared. She said, "I have so much pep I want to be doing something all the time." Edema, grade 2, of the ankles present before cortisone was given disappeared during the use of cortisone. The sedimentation rate (Westergren) fell 68 mm. in three weeks: from 80 to 12 (June 20 through July 11). Her over-all improvement was estimated at 95 per cent.

Withdrawal of Cortisone.—The patient had gained 14 pounds (6.4 Kg.) in twenty-three days, some of which was from retention of fluid. When use of cortisone was discontinued, she lost 8½ pounds (3.8 Kg.) in four days. On the

19. All such dates in these case reports are inclusive.

sixth day without cortisone, stiffness and soreness began to return, and the hands began to swell. After twelve days without cortisone pain on motion was still absent and walking was still easier, but many joints had swollen. About August 1 there was a flare-up of the articular condition. She could not undress or comb her hair without help. When she was dismissed as an outpatient, on August 6, her condition was about as it was before cortisone was given. The sedimentation rate had risen to 94 mm.

When she was reexamined on August 18, her arthritis was moderately severe. She could not put on her shoes, stockings or other clothes without help. Thereafter certain other substances were given, the results of which will be reported later.

Summary.—This patient's response to cortisone acetate was excellent.

CASE 7.—*Moderately severe rheumatoid arthritis; very marked and prolonged response to cortisone.*

A farmer's wife, aged 53 years, was admitted on Jan. 3, 1949. In January 1947 her left knee began to ache. In June 1948 her shoulders and elbows became affected. By September both knees were swollen, warm and red. Thereafter her fingers, wrists and neck were affected; her hands and arms were so painful that she could not pull the blankets over her at night, or make her bed until her room heated up. Squeezing a washcloth was difficult. Because of stiffness and pain she slept poorly and "watched the clock all night." Walking became so difficult in mid-October that she spent most of the time in bed. She could get around her room only by holding onto furniture. By about November 1 she became unable to walk. At the end of each day she reflected: "One more day of misery and pain is past."

The patient arrived in a wheel chair. Many joints were affected (shoulders, elbows, ankles and metatarsals) but mostly her wrists, which were moderately swollen, and her knees. Swelling, grade 2, and tenderness, grade 2 to 2+, of the knees were noted; flexion contracture of the knees was present (right 10 degrees and left 20 degrees). Roentgenograms of various joints, including the knees, showed osteoporosis but no destructive changes.

Between January 3 and 11 she remained in bed or in a wheel chair, mostly because of pain, partly because of instability and fear.

Use of Cortisone.—The patient was given cortisone (not the acetate), 100 mg. daily for twenty-five days (January 10 to February 3) (fig. 2). Fibrositic symptoms were gone within four or five days. During motion pictures made of her on January 10, just before her first dose of cortisone, she walked with great difficulty and could not climb the test steps; on January 13 she walked much better and climbed up the steps. On the fifth day swelling of right knee was reduced 2 cm. and she walked around her room. After eight days of use of cortisone she had no stiffness and no pain at rest or on use of joints except in the left knee. Only a slight limp remained. Whereas forced motion of the knees on January 10 produced marked pain (right grade 2+; left grade 3), twenty-four days later it produced no pain in the right and slight pain (grade 1) in the left. The sedimentation rate, which was 103 mm. on January 4, before cortisone was used, and 72 mm. after three days of its use (January 13), was normal (14 mm.) on February 3.

Withdrawal of Cortisone.—Cholesterol replaced cortisone February 4 and was given for fifteen days. On February 5 after she had walked one and a half hours, her left knee pained slightly for a couple of hours. On February 7 slight pain appeared in leg muscles and a wrist. But to our surprise the patient thereafter

maintained almost all her improvement and had little or no pain in the knees. She was dismissed February 26, considering herself still "90 to 95 per cent well." But the sedimentation rate rose to 58 mm. on February 14, after ten days without cortisone.

Follow-Up.—The patient has sent us many reports. After returning home she began at once the active life of a farmer's wife. Between March 1949 and the present (February 1950) she has done her own housework, cleaning, cooking, washing, ironing and sewing of clothes. She has often gone to town shopping. After "lots of walking" or such exertion as painting stairways she got tired and her knees ached. She planted the garden three times between April and June. She wrote: "I do my own housework and try to get in some extra work every day." Once she wrote "I put in a large garden, hoed weeds and painted the porch floor. I got tired I must have overdone a little." In view of such continuing reports we are inclined to accept her repeated estimate that she remains "90 to 95 per cent well."

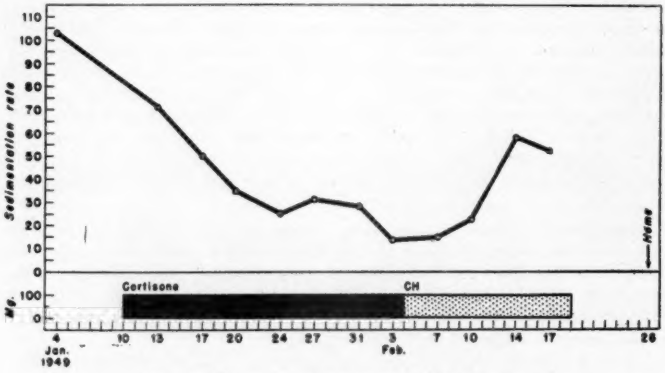

Fig. 2.—Curve of sedimentation rate in case 7.

Summary.—For reasons which are not clear and despite the prompt rise in her sedimentation rate, this patient's marked improvement has continued for about a year after use of cortisone was discontinued, much longer than that of any other patient. Her sedimentation rate was decreasing before cortisone was given, but there was at that time no associated clinical improvement and in other such instances the cortisone-induced remissions were not prolonged. It appears that something resembling a partial natural remission was induced.

CASE 9.—*Severe rheumatoid arthritis; very marked and rapid response to cortisone*

The patient, a woman 44 years old, was admitted to the hospital Jan. 17, 1949, because of rheumatoid arthritis of two years' duration affecting the wrists, elbows, shoulders, feet, ankles and knees. Much nocturnal and morning stiffness was present. At the clinic in September 1948 analgesics and physical therapy gave her

transient relief, but thereafter her condition worsened. Both hands were required to lift a coffee cup. She needed help getting out of bed and would shuffle to the toilet.

Moderate swelling and marked tenderness affected many joints. Both elbows were slightly flexed. Metatarsal joints showed tenderness grade 3 and were painful on forced motion. Roentgenograms showed swelling of soft tissues and slight destructive changes of finger joints. The sedimentation rate was 75 mm. on January 18 and 85 on January 19.

After January 16 acetylsalicylic acid was withheld, and the next two or three days were difficult and painful for her.

Use of Control Material.—Cholesterol was given for six days (January 19 through 24). At 10 p. m. on January 19 she was so stiff in bed that she could not move; two nurses helped her to assume a more restful position. But painful spasms in her arms and legs continued so that at 2 a. m. the nurses got her out of bed, and for thee hours she sat beside the bed with her arms and head on the bed. On January 20 she felt "helpless." She had to be lifted out of bed and helped into and out of a chair. Once on her feet she walked around her room with great difficulty. Swelling and tenderness of the ankles and metatarsals were increased. She could not get her shoes on or cut her food. Her swollen wrist was so painful she could not wear her wrist watch. For two days she felt better, but then she became worse again. She could only shuffle about her room. Her appetite was poor and she lost 6 pounds (2.7 Kg.) in six days. She needed help in dressing. The sedimentation rate was 82 mm.

Use of Cortisone.—Cortisone acetate was given for twenty-five days (January 25 through February 18): 300 mg. for one day; 100 mg. daily for thirteen days, and then small doses (50 mg.) daily for eleven days.[20] During the morning of January 25 she was taken to the clinic to have additional motion pictures made. At 2 p. m. she received her first dose of cortisone; then, tired from her trip to the clinic, she slept till about 5 p. m. Waking, she decided to write a letter. Heretofore because of painful, stiff fingers she had written poorly with a pencil, a few lines at a time. She found she could write easily, changed from pencil to pen and wrote six letters.

She went to bed without help, went right to sleep and awoke at 3 a. m. "feeling grand." She slipped her shoes on and for the first time in two years went to the toilet easily and without help. She was so thrilled that she called the night nurse; she was "too excited to sleep."

The next morning when we saw her she was excited and emotional. Her joints were markedly improved. In many joints tenderness grade 2, 2+ or 3 now had changed in two or three days to grade 1—. That day she washed the back of her neck "for the first time in two years," wringing her washcloth dry ("I've always left a dripping cloth"). The day previously her left hip was sore, but on this day to demonstrate her improved agility she lifed her left foot into the wash basin to show that she could wash it that way.

During the next two days muscular pain, stiffness and aching of joints disappeared. The left wrist still showed tenderness grade 1+. She slept "totally relaxed" and stated, "I have more pep than I've had in ten years." She ran down the hall to exhibit her ability. After a week of use of cortisone her appetite increased notably. On the ninth day (February 2) she was subjectively "100 per cent well" but tenderness grade 1— was present in one metatarsophalangeal joint.

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20. Graphic data in this case are shown in figure 3 of Hench, Kendall, Slocumb and Polley.[1a]

Other joints were painless even on forced motion. Flexion contractures of the elbows had disappeared. In view of the absence of "rheumatic pains," it was interesting to note that on this day her menses, always very painful, were as painful as ever. On February 7, after fourteen days of use of cortisone, joints were completely normal except for tenderness grade 1— of the left metatarsals. In the motion picture studio she ran over the testing stairs, whereas before she had received cortisone she had hobbled over them with great difficulty.

The sedimentation rate had fallen precipitously, 56 mm. in eight days (81 to 25 mm. from January 25 to February 1). It then rose slightly but became normal (17 mm.) on February 11.

Beginning February 8, 50 mg. of cortisone acetate was given daily for eleven days. That afternoon her feet swelled some and several joints ached. During the next ten days various symptoms recurred. On February 18, her eleventh day on these small doses of cortisone, she spent a restless, painful night and said, "For some reason I've been slipping for several days; I've slipped about 75 per cent. I suspect I'm not getting the same medicine."

Use of Cholesterol.—Injections of cholesterol were given for five days (February 19 to 23). The sedimentation rate rose to 76 mm. on February 23. Painful stiffness returned rapidly and articular swelling and tenderness more gradually. When motion pictures were taken again, the patient had great difficulty climbing the testing steps. She was dismissed February 26. Most of her subjective symptoms had returned, but she still retained some of her objective improvement.

Follow-Up.—After the patient returned home she got progressively worse for several months. Then chrysotherapy was begun. Improvement, slow at first, increased more rapidly, and in November 1949 when one of us saw her she was markedly improved, able to drive her car about town and to live a "fairly normal life."

Summary.—This severely disabled patient's response to 100 mg. doses of cortisone daily was so very marked and prompt that within two weeks she lost about 95 per cent of her symptoms. Daily doses of 50 mg. were ineffective, and symptoms returned. When cholesterol replaced the cortisone painful stiffness increased rapidly and constituted a "rebound relapse," although she retained some objective improvement for a short time.

CASE 13.—*Moderately severe rheumatoid arthritis; very marked and somewhat prolonged response to cortisone; negative response to compound A*

A housewife, 31 years old, was admitted to the clinic Feb. 22, 1949. Arthritis, which she had had for five years, had gradually affected her neck, wrists, fingers, knees, jaws, ankles and shoulders. In 1949 flexion of 20 degrees involved the right knee. Because of weak painful hands she could not open a door normally but wedged her arm between the door and the jamb first, and then opened it. She climbed a few stairs, one at a time. Getting off the edge of the bed in the morning was difficult. It took her 20 minutes to limber up. She lost her appetite and 10 pounds (4.5 Kg.). She had made numerous trips to hot springs.

She entered the hospital on February 26. Many joints were moderately swollen and tender; tenderness of a few, especially the metatarsals, was grade 2+ to 3. Roentgenograms of the right hand showed destructive arthritis. The sedimentation rate was 63 mm. on February 23 and 71 on March 1.

Use of Cortisone Acetate.—This was given for twenty-nine days (March 1 to 29); 300 mg. the first day; 100 mg. daily for thirteen days; 150 mg. daily for twelve days, and 100 mg. for the last three days (fig. 3).

On March 1 she could make only half-fists and could not walk on tiptoe barefooted. At 9:30 p. m. she received an initial dose of 300 mg. The next morning she woke almost entirely free of stiffness, got right out of bed and noted much less pain. She could make a tight fist and walk on tiptoe. The next day she had recovered various abilities and listed them proudly: lifting up a chair, dialing a telephone normally, wringing her washcloth dry, cleaning her face completely, "not just dabbing at it." Euphoria developed. Most of the soreness of the wrists and metatarsal joints was gone. She stated: "I am eating twice as much as usual." Within the next eleven days she lost an estimated 80 per cent of her rheumatic symptoms: The flexion contracture of the right knee decreased from 20 to 5 degrees. The sedimentation rate fell 45 mm. in two weeks—from 71 to 26 mm. (March 1 to 15).

To see whether her residual symptoms could be eliminated, the daily dose was increased to 150 mg. for twelve days (March 15 to 26). Improvement continued.

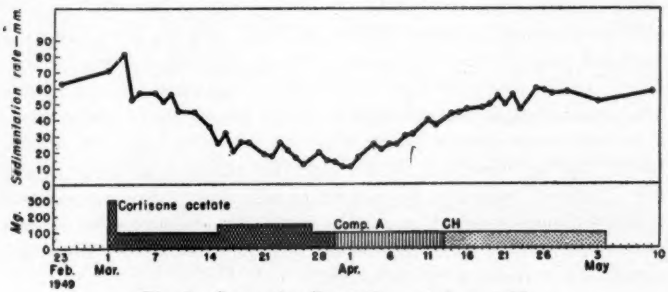

Fig. 3.—Curve of sedimentation rate in case 13.

She was ravenous, but she gained only 4 pounds (1.8 Kg.) in twenty-three days. She walked around town; after a mile (1,600 meters) her feet ached slightly. Sometimes she slept soundy all night; sometimes she woke and found it hard to go back to sleep. Asked whether pain had kept her awake she said: "No, I was just thinking about the change that has happened in me." Her menses, always irregular, appeared on March 8 and again sixteen days later (March 26) "not unusual for me." After twenty-six days of use of cortisone the sedimentation rate became normal (12 mm.). She felt "almost completely well" and free of all symptoms during ordinary activity. There was no pain or tenderness on deep pressure or even forced motion. But the right knee flexed 5 degrees, and barely perceptible swelling remained in a few joints. During the last three days she received 100 mg. of cortisone daily.

Effect of Compound A (11-Dehydrocorticosterone).—This was given for fourteen days, 100 mg. daily (March 30 to April 12). The sedimentation rate rose slowly, but the patient retained all of her improvement for two weeks.

Use of Control Solution.—Cholesterol was given daily for twenty-one days (April 13 to May 3). About April 16 slight aching in the wrists returned and walking barefooted on tiptoes began to be difficult. But for days after cortisone

was replaced by compound A the patient was almost symptom free. The sedimentation rate continued to rise gradually. There was a slight increase in symptoms and signs, but when she was dismissed, May 10, many joints were still subjectively and objectively normal and no articular swelling was present.

Follow-Up.—At home the patient assumed the full duties of housekeeping and was on her feet "at least seven hours a day." Despite this her condition remained relatively unchanged for about four weeks. Then her appetite decreased, slight stiffness developed, and a hand swelled slightly. Three months after the use of cortisone was discontinued, she estimated that she still maintained half of the effect of cortisone.

On July 20 she wrote that having tried for three years to become pregnant she was thrilled to find that she was now a few weeks pregnant. She wondered whether the cortisone was partially responsible. Then she began to experience the beneficial effects of pregnancy, needed no acetylsalicylic acid and had no morning stiffness. During the next five months of pregnancy she led an active life, which included a fishing trip. Her relief varied from 65 to 80 per cent. Her pregnancy is near full term.

Summary.—The effect of the initial high dose of cortisone given at 9: 30 p. m. became apparent eight hours later. It is not certain that the increased doses (150 mg.) augmented the excellent effect of the 100 mg. doses. In this case relief lasted longer than usual after use of cortisone was discontinued, and the prolongation might be ascribed to compound A. From our experience with compound A in other cases we do not believe that the compound A prolonged the effect of cortisone in this case. Although symptoms did not return until about the time cholesterol replaced the compound A, the sedimentation rate began to rise as soon as cortisone was withheld and did not increase more rapidly after compound A was replaced by cholesterol.

CASE 22.—*Severe rheumatoid arthritis of spinal and peripheral joints; very marked effect of cortisone*

A man, 22 years old, was admitted to the hospital Aug. 9, 1949, because of rheumatoid arthritis of the spine and peripheral joints of three to eight years' duration. In 1941 muscles of a thigh had ached for two months; the other thigh was similarly affected for one month in 1943. Although roentgenograms revealed no abnormality, these attacks may have been the first evidence of (impending) spondylitis. Painful stiffness affected the patient's neck in December 1946 and his thighs in November 1947. After July 1948 aching and stiffness progressively affected the hips, thighs, shoulders, spine, ankles and knees. The sedimentation rate was elevated. It was hard for him to put on his socks and shoes. Difficulty in combing his hair was solved by wearing a "crewcut."

Motion was considerably limited in the neck, shoulders, spine and knees. He could abduct the right arm only 65 degrees. The knees were slightly swollen. Roentgenograms revealed bilateral sacroiliac arthritis. Sedimentation rates were 77 mm. on August 15 and 87 mm. on August 24.

A test of adrenal response to a single intramuscular injection of ACTH (25 mg.) was made on August 22. Within a half hour stiffness, weakness and pain had decreased.

Use of Cortisone Acetate.—This was given for thirty-two days, 100 mg. daily (August 24 to September 24). Improvement was gradual. By the fourth day of administration stiffness and pain were lessened. In fourteen days aching had disappeared and appetite was increased. By the fourteenth day few painful symptoms remained. Before use of cortisone was discontinued, the patient could rotate his neck to 90 per cent of normal (previously 50 per cent), abduct his right shoulder to 100 degrees (an increase of 35 degrees), comb his hair and walk or run up stairs. Walking one flight of stairs had previously been difficult and taken ten minutes; now it took one minute. Stooping, he came within 12 inches (30 cm.) of the floor, 6 inches (15 cm.) closer than previously. He lost an estimated 90 per cent of his symptoms. Slight pain on motion of some joints was still present. He ate between meals and gained 20 pounds (9.1 Kg.). His face was full from his general gain in weight, not from hypercortisonism. There was no diminution of libido or potentia.

He had had seasonal hay fever for years and had it when use of cortisone was begun. Within two hours after the first injection his nose "opened up." During the next week he sneezed only occasionally; thereafter he had no symptoms of hay fever. The hay fever season was still on; pollen counts were still high. The sedimentation rate dropped 65 mm. in thirty-one days—from 87 to 22 mm. (August 24 to September 23).

Withdrawal of Cortisone.—On September 26, the patient's first day without cortisone, he received another injection of 25 mg. of ACTH; within twenty minutes he lost all residual pain. Within nine days stiffness and fatigue increased. After another test with ACTH, on October 7, he had "the first good day since my daily injections were stopped"; within thirty minutes pains were markedly relieved and the relief continued for ten hours, during which he was able to stoop to within 8 inches (20 cm.) of the floor. But on this day (twelve days without cortisone) his sedimentation rate was 81, an increase of about 50 mm.

On December 9, eleven weeks after use of cortisone was discontinued, he had maintained an estimated 50 per cent of its effect.

Summary.—The patient's response to cortisone was very satisfactory. His rheumatoid spondylitis responded, as did his rheumatoid arthritis of peripheral joints and his symptoms of hay fever. No side effects of any kind developed. For about three months after the course of cortisone, half of its effects continued.

CASE 8.—*Severe rheumatoid arthritis; very marked response to cortisone in full doses; poor response to small doses*

A physician, 62 years old, was admitted to the clinic on Dec. 23, 1948. Between 1933 and 1945 he had had many attacks of episodic rheumatoid arthritis. Since October 1948 his hands and feet had been swollen, painful and stiff.

At the clinic the patient received symptomatic therapy for two weeks without much relief. He was admitted to the hospital Jan. 10, 1949. He walked slowly and carefully because of painful knees, ankles and metatarsal joints. Raising his arms was difficult and painful. He could rise from a chair only by using his arms. His hands and feet were moderately swollen, and tenderness of the fingers and metatarsals grade 2+ and 3 was present.

On January 16, his daily physical therapy and use of acetylsalicylic acid were discontinued; pain and stiffness increased considerably. On January 18 he had his "worst night in months" and had to be helped out of bed the next morning. The sedimentation rate was 50 mm.

Cortisone.—First Course: This was given for nine days (January 19 to 27): 300 mg. the first day; 100 mg. daily for eight days (fig. 4). On January 19 at 3 p. m. he was given 300 mg. intramuscularly. At 10:30 p. m. he fell asleep and "slept like a log" till 5 a. m. (January 20). He got out of bed easily and felt little stiffness or pain. That day he could raise his arms "perfectly normally," could make a full fist for the first time in weeks and was ravenous. He walked two hours without pain. Tenderness of finger joints was already reduced from grade 2+ to 1.

Within four days he lost all aching, almost all the stiffness of muscles and joints and most of the articular tenderness and pain on motion. He said, "To me, a physician, the change is phenomenal." Within three more days many joints were symptom free and painless to deep pressure and forced motion. A few joints exhibited tenderness grade 1—. He walked around downtown. "I'm on top of

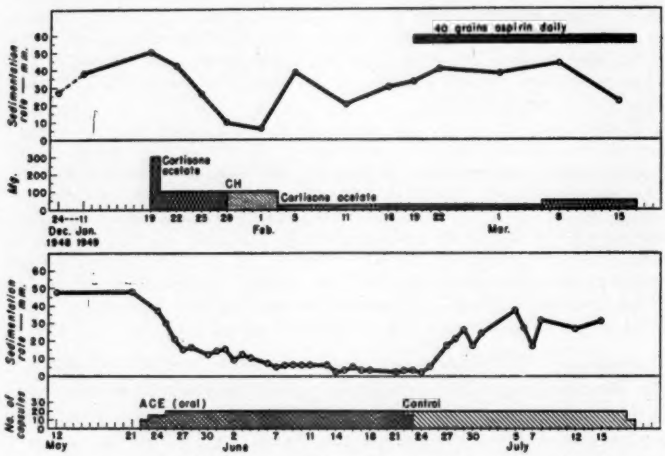

Fig. 4.—Curve of sedimentation rate in case 8.

the world," was his comment. The swelling of his hands almost completely disappeared.[21] The sedimentation rate fell 40 points to 10 mm. on January 28. He estimated that he had lost 95 per cent of his symptoms. Motion pictures were taken again; he walked rapidly over the testing steps, whereas a few days previously he could hardly scale them. He wanted to demonstrate his ability to run, but because of ice and snow outside we had him "run in place" in the studio.

Use of Control Solution.—For six days after cortisone was withdrawn cholesterol was given (January 28 to February 2). The sedimentation rate remained low for four days—6 mm. on February 1. But symptoms remained in abeyance only two days and then returned rapidly so that after five days without cortisone he had to be helped out of bed. Fever (temperature 101 to 102 F.) was present

21. Photographs of this patient's hands before, during and after use of cortisone are shown in figure 1 of Hench, Kendall, Slocumb and Polley.[1a]

for two days. Within five days an 85 per cent relapse occurred. The sedimentation rate rose to 38 mm. on February 5.

Cortisone.—Second Course, Small Doses: In an attempt to find a small maintenance dose, 25 mg. of cortisone was given daily for thirty-one days (February 3 to March 5). Muscles were less stiff but joints were unchanged, and the patient got progressively worse.

To determine whether these small doses of cortisone could be enhanced thereby, acetylsalicylic acid, 40 grains (2.6 Gm.) daily, was given from February 19 to March 16, but no improvement resulted. He needed help getting into and out of bed and was so stiff he could not shave till late in the morning. On March 3 he "felt 110 years old."

Between March 6 and 16 the daily dose of cortisone was increased to 50 mg. Partial relief resulted. The sedimentation rate decreased from 43 to 22 mm. (March 8 to 15). The patient was able to walk, climb stairs, get into a tub and into and out of bed more easily. Aching and stiffness were reduced to about a third of that on admission. But tenderness and pain on forced motion were as before use of cortisone.

No side effects developed; sexual impulses were not reduced.

Within a few days after dismissal on March 16 he regained most of his disability. Morning stiffness was great; he set the alarm so that he could take acetylsalicylic acid at 3 and 7 a. m. in order to get up more easily about 8 a. m.

Thereafter an adrenal cortex extract was used; the results will be reported later.

Follow-Up.—The patient continued to have transitory articular flare-ups, but after six months without cortisone he still retained an estimated 20 per cent of his improvement.

Summary.—This patient was improved very markedly and rapidly by 100 mg. doses of cortisone and relapsed quickly when they were discontinued. Small doses (25 mg. daily) gave no significant relief. Doses of 50 mg. daily gave partial relief from stiffness but did not affect articular swelling, tenderness and pain. Even with supplemental acetylsalicylic acid (40 grains daily) the 25 and 50 mg. doses of cortisone did not control symptoms.

CASE 19.—*Severe rheumatoid spondylitis; marked improvement from cortisone*

A physician, 30 years old, had had rheumatoid spondylitis for eleven years. In 1938, pain low in the back and sciatica developed. Rest in bed, then crutches, later a cast and then a brace were necessary. In 1942 backache increased after he played tennis. Thereafter the entire spine was affected. Since 1945 he had had pains in the chest, constant backache and some sciatic pain. He was chronically fatigued and "mentally depressed." Morning stiffness was so marked that he "inched out of bed." It was difficult for him to put on his socks or stoop to get into or out of a car. He had not been able to take a tub bath for six years.

When admitted May 24, 1949, the patient held the entire spine stiff as he walked. To turn, he had to turn his whole body. Limitation of motion of the cervical part of the spine was marked; of the thoracic and lumbar parts, almost complete. The entire spinal region was tender to percussion. On stooping he could only get 21 inches (53 cm.) from the floor. Peripheral joints were not affected.

Sedimentation rates varied between 60 and 83 mm. Roentgenograms showed destructive arthritis of both sacroiliac and lumbar apophysial joints.

Effect of Cortisone Acetate.—This was given for sixty-six days (June 6 to August 10); 300 mg. the first day; 100 mg. daily thereafter (fig. 5). During the first day there was no change, but he slept well that night. The next morning he got out of bed much more easily. That night he only slept four and a half hours but got right out of bed the next morning without fatigue. Pain and tenderness on percussion were much less; he said, "about half gone." On the fourth day he could sit with his legs crossed normally and easily reach his foot. Two days later he felt as if he had "no arthritis." Chest expansion increased from ½ to 1½ inches (1.3 to 3.8 cm.). He could rotate his neck 75 degrees to each side and he could bend 11 inches nearer the floor than previously. That night he slept only three hours: "I was just thinking about things." His appetite increased markedly. He increased his activity and fished for several hours one day without subsequent stiffness. About July 1 he noted for a few days dull lumbar or sacroiliac pain after jarring. On July 9, after thirty-three days of use of cortisone he had no morning stiffness and no spinal tenderness or pain but motion was

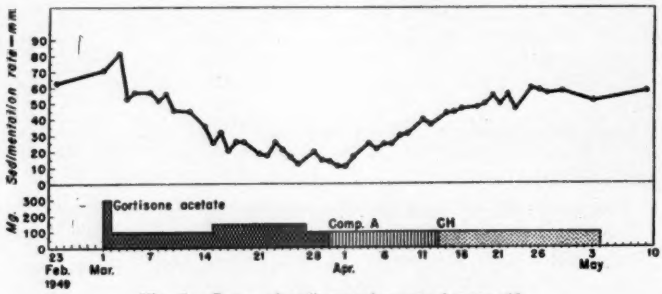

Fig. 5.—Curve of sedimentation rate in case 19.

still limited. After about five weeks of use of cortisone he had lost 90 per cent of his symptoms.

During the next two weeks his increased activity produced mild backache. Rather than diminish his activities, he decided to wear his old Taylor brace during his more active hours. He walked an average of a mile daily and could drive his car. One day he drove to Minneapolis (about 90 miles [145 kilometers] away), walked 4 or 5 miles (6.5 or 8 kilometers) about town and (with use of the brace) had no fatigue or pain. After five weeks of use of cortisone mild acne developed on the shoulders and upper part of the chest. No edema was noted. Libido and potentia were not affected. The sedimentation rate fell from 70 to 32 mm. after eighteen days of use of cortisone (June 6 to 24) but did not continue to fall and thereafter varied usually between 39 and 58 mm.

Withdrawal of Cortisone.—Two days after use of cortisone was stopped, the patient had sciatic pain for ten minutes. The next night he woke four or five times because of pain. He could now bend only to within 16 inches (41 cm.) of the floor, as compared with 10 inches previously. Within the next two weeks most of his symptoms returned. The acne disappeared within six weeks. Weakness returned and for two weeks was greater than before use of cortisone.

Follow-Up.—The weakness gradually disappeared. Loss of appetite, anorexia and weight loss of 16 pounds (7.3 Kg.) within three months accompanied the return of arthritis. When the patient was seen at the clinic on Jan. 13, 1950, his spine was about as it had been before cortisone was given.

Summary.—The response during the first five weeks was good but incomplete. A daily dose of 100 mg. did not control all symptoms or lower the sedimentation rate to normal.

CASE 18.—*Very severe rheumatoid arthritis and spondylitis; very marked and prolonged effect of ACTH given for eighty-seven days*

A man, 38 years old, was admitted to the hospital on April 25, 1949, because of rheumatoid spondylitis for six years and arthritis of peripheral joints for two years. Symptoms were aggravated by driving a car and physical labor. He had to quit work as an oil driller. Various treatments were ineffective.

Early in 1947 metatarsal joints became swollen and painful, and they remained so; backache continued. In March 1949 other peripheral joints became affected. Fever and malaise developed. The patient's appetite was poor, and he lost 10 pounds (4.5 Kg.) in a month. On arrival at the clinic he had been practically bedridden for a month.

The patient was a big man, weighed 225 pounds (115.6 Kg.) and stood 6 feet 3½ inches (191.77 cm.). His temperature was 101 F. The spine was painful and markedly limited in motion; the lumbar curve was flattened. Many peripheral joints were affected. Swelling of grade 2 was noted in an elbow, wrist and knee and of grade 3 in the ankles and metatarsal joints. Tenderness of grade 2 was present over the sacroiliac joints; of grade 3, over the elbows, wrists, a knee and the metatarsals, and of grade 3+, over the ankles.

Roentgenograms revealed destructive arthritis of metatarsal and sacroiliac joints. The sedimentation rate was 126 mm. on May 4.

Course Before ACTH.—Rest in bed was continued of necessity. Unaffected joints became involved. Morning stiffness lasted four or five hours. The patient could not shave himself, put on his pajamas, comb his hair or wring out a washcloth. Two attendants helped him to the toilet; he got off the toilet by grabbing the door knob and pulling himself up. He did not attempt tub baths. He took 75 grains (5 Gm.) of acetylsalicylic acid a day. Sedimentation rates were 125 mm. on May 18 and 119 mm. on May 20.

On May 20 he was unrelieved after four weeks of symptomatic treatment. He had to feed himself with his left hand. He could not hold a glass of water or even turn on the radio with his right hand. "At times I can't even hold a newspaper." He could not tear a piece of paper, take matches out of a match clip or light his cigaret. He was taken in a wheel chair to the motion picture studio. With great difficulty he climbed up the three test steps but could not walk down them. "It hurts so much I feel sick at my stomach."

Daily temperatures were usually 99 to 100F.

Use of ACTH.—This was given in varying doses daily for eighty-seven days (May 21 to August 15). Daily doses of 70 mg. (35 mg. twice a day) were given for eight days, 105 mg. for three days, 140 mg. for three days, 125 mg. for one day, 120 mg. for twelve days (June 5 to 16), 75 mg. on June 17, 45 mg. on June 18, 75 mg. on June 19, then 90 mg. (30 mg. three times a day) for nine days through June 28, thereafter 100 mg. daily for the next 48 days (June 29 to August 15).

The morning after the first injection of ACTH stiffness and pain were less and the patient could get his right hand to his face and comb his hair. For the first time in two weeks he got out of bed and sat in a chair. During the next four days, improvement was moderate; the appetite improved markedly. He could go to the toilet without help. Articular swelling and tenderness receded. After five days of use of ACTH he estimated his relief at "50 per cent at least." He could walk through the hospital corridors and get into and out of a low chair, but the sedimentation rate was still rapid, 122 mm. on May 28. Therefore the doses of ACTH were increased. Except for "a feeling of fulness and fluttering in the neck" for two days, he had no other side effects from these higher doses. The sedimentation rate fell to 55 mm. on June 13. The patient could walk up one flight of stairs. A second motion picture was taken; whereas formerly he climbed the test steps so slowly that it took 100 feet (30.5 meters) of film to record it, he now got over them so rapidly that it required only 5 feet (1.5 meters) of film. Swelling and tenderness of joints was now generally slight (grade 1 or 1 +); many joints were symptomless.

About June 10 scattered areas of pigmentation appeared in palmar creases and in a scar over the right knee.[22] There was freckling of the face and neck. The pigmentation increased. Although this patient excreted less 17-ketosteroids and corticosteroids than did other patients given ACTH, the amounts in the urine indicated that his adrenal glands were capable of responding to ACTH and that the pigmentation was not due to Addison's disease. The lots of ACTH being used were analyzed by Dr. Alexander Albert and found to contain melanophorin, contamination from the pituitary pars intermedia. Hypophysectomized frogs given injections of some of this batch of ACTH became deeply pigmented. When use of ACTH was discontinued, pigmentation gradually faded and disappeared during September.

To see whether smaller doses would suffice, the total daily dose of ACTH was temporarily reduced from 60 mg. twice daily to 15 mg. thrice daily (June 18); but there was a flare-up of the articular condition, the sedimentation rate rose quickly from 48 to 89 mm. (June 20). The dosage was then gradually increased to 100 mg. daily, and the hormone was given in divided doses every six hours instead of every eight or twelve hours. The patient improved again, and sedimentation rates fell to 21 mm. on July 19 but some articular symptoms persisted.

Injections of ACTH in oil were then given two or three times daily intragluteally (total daily dose 100 mg.) for seven days in an attempt to provide evener absorption. But the suspension was ineffective; symptoms increased, and the sedimentation rate rose from 21 to 50 mm. (July 19-25). Hence injections of ACTH in saline solution every six hours were begun again. By August 3 the patient had lost 75 per cent of his disability and felt better than at any time during the previous two years.

Between August 1 and 12 areas of right gluteal tenderness were noted at sites of injections and an abscess related to the oil menstruum was drained. Swelling had disappeared from some joints and was slight in other joints. The patient had no pain at rest or on voluntary motion and slight pain on forced motion of an elbow, wrist and knee. The over-all relief was estimated at 85 per cent (fig. 6).

22. (*a*) Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199 (Feb.) 1950. (*b*) Photographs of this pigmentation are shown in figure 4 of this article.

Fig. 6 (case 18).—Synovia of the right knee before ACTH was given: (*a*) May 18, 1949, showing the marked lymphocytic cellular reaction and edema, to be compared with (*b*) Aug. 11, 1949, after eighty-two days of use of ACTH, showing the replacement of the lymphocytic inflammatory reaction by fibrosis. Hematoxylin and eosin; × 65.

The patient had no significant side effects: "Fulness in the neck" was present for a couple of days. The blood pressure fluctuated daily (systolic 110 to 150 mm.; diastolic 60 to 90 mm.) without respect to the ACTH. There was no acne, increased hirsutism or edema.

Withdrawal of ACTH.—The last injection was given August 15. The sedimentation rate rose rapidly to 102 mm. on August 23 and then fell to 73 mm. on August 29. At the time of his dismissal, August 29, two weeks after use of ACTH was discontinued, he still retained most of his improvement.

Follow-Up.—Five months after ACTH was withdrawn the patient still retained most of the antirheumatic effect (Jan. 15, 1950). He was living an active, relatively normal life, which included long automobile and hunting trips.

Summary.—This severely disabled patient was markedly, though not completely, relieved during the use of ACTH daily for 87 days. Thereafter he maintained most of his relief to date (five months). Best results were obtained when 25 mg. was given every six hours. Two incidents occurred: Transient pigmentation of skin resulted from melanophorin in a lot of ACTH used; a gluteal abscess developed after use for a few days of ACTH in oil.

CASE 5.—*Very severe subacute rheumatoid arthritis of peripheral joints and spine; very marked effect of cortisone*

A trucker, 34 years old, was first admitted to the hospital Oct. 28, 1948. Between March and July 1948 the left metatarsal joints became intermittently sore. He awoke August 7 with painful stiff shoulders. Within a week many peripheral joints became involved. He quit work and had various treatments, with little effect. During the next three months, he became progressivily worse, weak and fatigued, lost his appetite and 35 pounds (15.9 Kg.). He lost much sleep because of pain at night; to keep the weight of bedclothes off his feet, he used a cradle.

On admission to the hospital many joints were tender, stiff and swollen. Rheumatoid nodules were present at the elbows and left wrist. Roentgenograms showed early destructive changes of the right sacroiliac joint and osteoporosis of bones of the hands, wrists and knees. The sedimentation rate was 70 mm. on October 27. During four weeks of symptomatic treatment he did not improve. It was hard for him to get out of bed. The temperature was occasionally 100 F. He went home for five days to arrange his affairs so that he could return for further study.

When the patient entered the Metabolism Unit, Nov. 28, 1948, he could abduct the right shoulder only to 90 degrees and the left to 45 degrees. The right elbow was flexed 10 degrees; the left, 15 degrees. All medication, including acetylsalicylic acid, was withdrawn. As a result, he slept practically none the first night and only three hours the second night. Despite administration of 2½ grains (0.162 Gm.) of codeine the third night, pain was poorly controlled and he got little restful sleep. Because of weakness, exhaustion and pain he was thereafter given 40 grains (2.6 Gm.) of acetylsalicylic acid daily while metabolic studies were conducted. For a week he had fever (temperature 99 to 101 F.) and his joints were so painful that codeine was often required. He was out of bed an hour daily, long enough to have his bed made and to go to the toilet. He shuffled around the room and rose from chair with difficulty. He was exhausted and felt "terrible." Sedimentation rates varied from 89 to 65 mm.

Use of Control Material.—Cholesterol was given for six days (December 18 to 23) (fig. 7). The composition of this solution was unknown to the three clinicians in charge of the patient and was known only to Dr. Kendall and to Dr. Sprague. No subjective, objective or laboratory improvement occurred. Sedimentation rates were 65, 69 and 65 mm. on December 18, 21 and 24, respectively.

Effect of Cortisone.—On the morning of December 24 several joints were moderately swollen and stiff and many were markedly tender, especially those

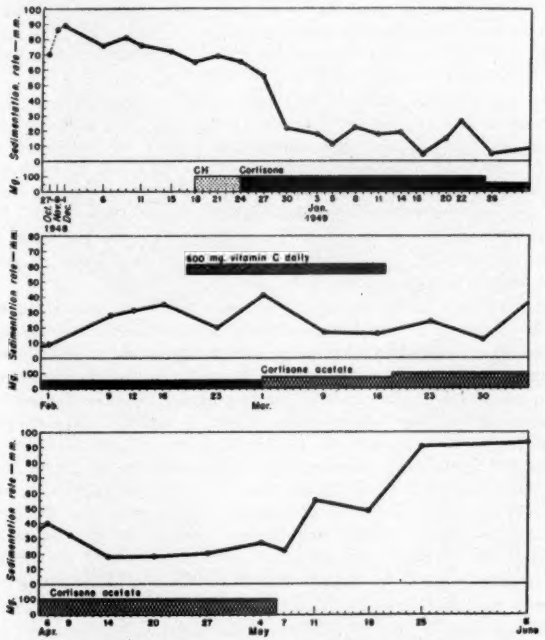

Fig. 7.—Curve of sedimentation rate in case 5.

of fingers and metatarsals. As usual, an injection was given that morning and another at 8:00 p. m. The patient did not waken until 7 a. m. December 25 and was surprised to find that it was light outside and that he had slept all night. That morning he got right up and walked off "without having to see whether my knees and ankles would take it." He did not have to hang onto anything, and he had no stiffness or soreness to speak of. He was able to put on his shoes this morning for the first time in a month.

He put on street clothes and was up two hours in the morning and most of the afternoon, visiting people in various hospital rooms, even climbing stairs. That evening he read several magazines, which he had not been interested in doing previously.

The next day stiffness had disappeared; articular tenderness was diminished. The clinicians evaluating the results concluded that the patient had been given a control solution until the morning of December 24 and that cortisone had then replaced the cholesterol. This proved to be correct. Cortisone or cortisone acetate was given daily for one hundred and thirty-three days (four and one-half months) from Dec. 24, 1948 through May 5, 1949. Daily dosage was as follows: 100 mg. for thirty-two days, through January 24; 50 mg. for thirty-five days, through February 28; 75 mg. for seventeen days, through March 17, and 100 mg. for forty-nine days, through May 5.

The patient's appetite improved immediately, and after three days of use of cortisone he was hungry between meals and could hardly wait for breakfast. His wife, who had not seen him for two weeks, visited him on this day and exclaimed, "What has happened is unbelievable."

He became euphoric and lay awake until midnight. When asked whether it was because of pain he said, "No. I'm not sleepy and I just lie awake thinking about things." On New Year's day, after eight days of use of cortisone he was practically free from rheumatoid manifestations; an estimated 90 to 95 per cent regression of his disease. He had no tenderness, stiffness or pain at rest or on motion. Flexion contractures of shoulders and elbows had disappeared. Articular swelling had practically disappeared. The sedimentation rate had fallen 43 mm. in six days—from 65 to 22 (December 24 to 30). It was 11 mm. on January 5 and rose again to 22 mm. on January 8.

Most of the time during the next three weeks the patient was subjectively and objectively almost well. There was no definite difference in the response when the total daily dose was divided into two or four smaller doses or given once daily. The sedimentation rates fluctuated between 22 and 5 mm., rose to 26 (January 22) and then fell to 5 mm. (January 26). It was decided to reduce the daily dose to see whether smaller doses would suffice. Hence 50 mg. was given daily for the next thirty-five days (January 25 to February 28). There seemed to be no significant difference in his response to a morning injection of 50 mg. than to a morning and evening injection of 25 mg. each. For three more weeks his subjective and objective condition was very satisfactory. His appetite was "tremendous"; occasionally his hunger distressed him because, being in the Metabolism Unit on a controlled diet of about 2,400 calories, he was not permitted extra food. His weight remained constant at about 61 Kg. from December 24 to January 24.

Most of the time he was symptom free or practically so, but frequently he had mild soreness in one or another joint, more so than when he received 100 mg. of cortisone daily. After being removed from the Metabolism Unit on January 25 and allowed to eat at will, he often ate double servings and his weight rose from 139 to 153 pounds (63 to 69.4 Kg.) on March 1. He sometimes walked for two hours and as much as twenty blocks. His shoes, bought when his feet were swollen, were now too large. But a daily dose of 50 mg. appeared to be suboptimal, not only because there were transient residual symptoms but because the sedimentation rate was steadily increasing.

Before increasing the dosage of cortisone it was decided to supplement it with 600 mg. of vitamin C a day, given orally, to see whether this would augment the effectiveness of the small suboptimal doses of the hormone. The vitamin C was given for twenty-six days (February 19 to March 16). But the right elbow began to flex slightly, and a wrist became more painful and tender than any joint had been for many weeks. Therefore the daily dose of cortisone (now cortisone

acetate) was increased to 75 mg. for the next seventeen days (March 1 to 17). Within a few days arthritic symptoms and signs were again minimal and the sedimentation rate decreased to 16 mm. The patient continued to gain weight, walked as much as 2 miles (3.2 kilometers) some days and felt "95 per cent well" (fig. 8).

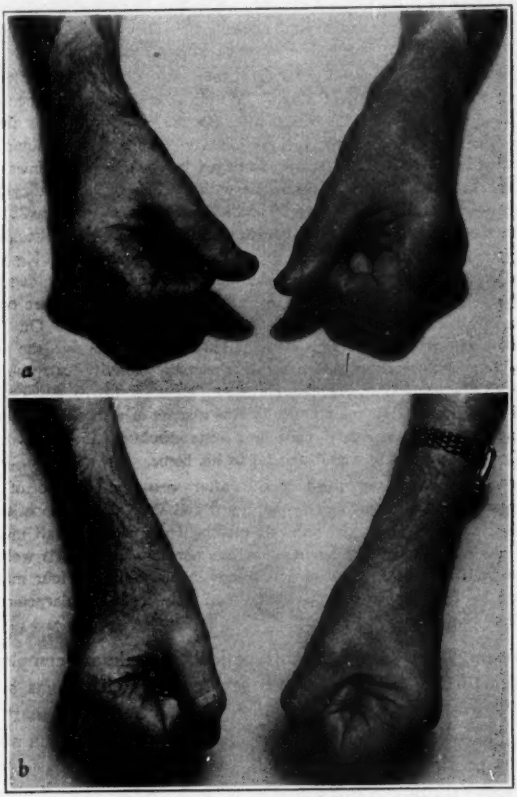

Fig. 8 (case 5).—Hands of patient: (*a*) Dec. 15, 1948, showing swelling and inability to make a tight fist before cortisone was given; (*b*) March 15, 1949, after eighty-two days of use of cortisone, showing reduction of swelling and ability to make a complete fist.

Use of vitamin C was then discontinued (March 16). When the daily dose of cortisone acetate was increased and continued at 100 mg. again (March 18 to May 5) the patient once more became almost free of symptoms. He remained thus except for a short flare-up (with a sudden change in sedimentation rate from 12 to

40 and back to 17 mm.) which occurred about April 5. He continued to gain weight. His weight before illness was 170 pounds (77.1 Kg.); on admission to the unit on November 28 it was 144 pounds (65.3 Kg.); on May 7 it was 163 pounds (73.9 Kg.). The sedimentation rate remained normal.

During these weeks the following facts were noted: Previously shaving only two or three times a week, the patient had to shave daily and had his hair cut every two instead of every four weeks. He noted transiently increased perspiration. Libido and potentia were normal and unchanged. They was no acne, edema or hormonal rounding of the face. The blood pressure remained normal.

Withdrawal of Cortisone.—Use of cortisone was discontinued after May 5. The patient became an outpatient May 7. Within four days the sedimentation rate increased from 22 to 55 mm. Two days after the use of cortisone was discontinued a wrist became sore. Thereafter various joints were involved in minor flare-ups, but the patient remained fairly active, managed his buiness, sometimes walked 2 miles a day, slept well and was comfortable with the help of acetylsalicylic acid.

Sedimentation rates were between 90 and 95 mm. (May 25 to June 22). During this month the arthritis increased slightly. The patient lost appetite; his weight was 147 pounds (66.7 Kg.) on June 22, a loss of 17 pounds (7.7 Kg.) in about seven weeks. Abduction of the shoulders became limited to 90 degrees. But objectively, the joints were still much less affected than before the use of cortisone and the over-all relief on June 22 was still about 80 per cent. On July 6 the sedimentation rate reached the high value of 126 mm. Despite this, the patient had few subjective or objective evidences of rheumatic activity two months after cortisone was withdrawn. He thought that "about 5 to 10 per cent" of his arthritis had returned. His main difficulty was a sense of weakness and exhaustion, which was probably hormonal; neurologic tests disclosed no objective evidence of muscular weakness. He was dismissed to his home.

Follow-Up.—During the third month after cessation of use of cortisone the muscular weakness progressively improved and the patient's appetite returned to normal. In the past six and one-half months (nine and one-half months since cortisone was discontinued) he has regained his normal weight, feels well, takes no medication and has had no transitory flare-ups in his joints for four months. He stated that he felt 95 per cent well and had only a little enlargement in two finger joints (February 1950).

Summary.—On admission this patient was almost completely disabled by arthritis and pain was so severe that codeine was sometimes required. From cortisone he obtained such prompt and marked relief that within a week symptoms had practically disappeared and sedimentation rates became normal. As long as the daily dose was 100 mg., marked relief continued but doses of 50 and 75 mg. were less effective. The patient tolerated well the relatively prolonged use of cortisone; the only side effect noted was mild excess growth of hair.

After use of cortisone was discontinued, his joints remained almost well for three weeks and were then moderately troublesome for a month. Then he spontaneously regained almost all the former relief in the face of continually increasing sedimentation rates. Postwithdrawal exhaustion was probably hormonal.

GROUP 2: MARKED ANTIRHEUMATIC EFFECT WITH MILD SIDE EFFECTS

CASE 17.—*Severe rheumatoid arthritis and spondylitis; marked effect from ACTH*

A student, 23 years old, was admitted to the clinic March 23, 1949, because of articular disability for six and one-half years. In 1942 and 1943 mild pain on abduction and nocturnal aching affected a shoulder and became chronic. Early in 1944 a "bursa" was removed surgically from his shoulder. After three weeks of postoperative immobilization, abduction of the shoulder remained limited to 90 degrees. Later that year several peripheral joints, back and hips became affected. In 1945 he became almost well and entered into military service. Marching aggravated metatarsal tenderness, and the patient was discharged after two months. In April 1948 the back, jaws and other joints were affected. In six

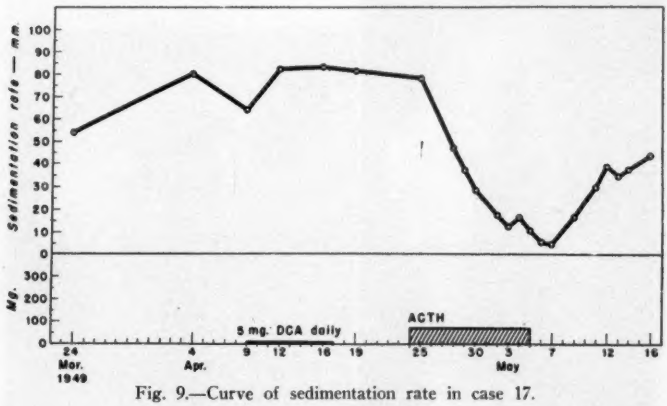

Fig. 9.—Curve of sedimentation rate in case 17.

months he lost 20 pounds (9.1 Kg.) and 1¼ inches (3.2 cm.) in height. Many remedies were ineffective.

The patient was admitted to the hospital March 26. Many joints were involved. Tenderness was marked in the knees, metatarsals and thoracic and lumbar portions of the spine. Swelling was mild in the knees, marked in the metatarsals. Motion in the lumbar and thoracic portions of the spine was markedly limited, grade 3. Roentgenograms revealed destructive arthritis of the sacroiliac, left shoulder and a finger joint. Sedimentation rates were 54 mm. on March 24, 80 mm. on April 4 and 64 mm. on April 9.

The patient could sleep only three or four hours nightly. It was difficult for him to turn over or to sit up in bed, and his appetite was poor.

Use of ACTH.—Doses of 35 mg. were given twice a day for eleven days (April 24 to May 4) (fig. 9). Within forty-eight hours he lost all pain at rest and much of his stiffness and soreness. Improvement continued so that after the eleven days of use of ACTH most of the subjective manifestations were relieved and, except for residual stiffness of the spine, the only objective residues were swelling grade 1— of the knees, which were painless to deep pressure,

and tenderness grade 1 — of the left metatarsals and left mandibulotemporal joint. The over-all relief was an estimated 75 per cent (fig. 10).

During the use of ACTH the sedimentation rate fell precipitously: 67 mm. in eight days, from 78 to 11 mm. (April 24 to May 3). The patient's appetite was insatiable; on May 5 he ate two breakfasts and two dinners. He gained 16½ pounds (7.5 Kg.), much of which was probably due to fluid retention. During the use of ACTH there was no significant change in blood electrolytes.

Withdrawal of ACTH.—The sedimentation rate continued to fall to 4 mm. two days after administration of ACTH was discontinued; it then rose to 43 mm. on May 16. On May 6, the second day without ACTH, headache, dizziness, sore

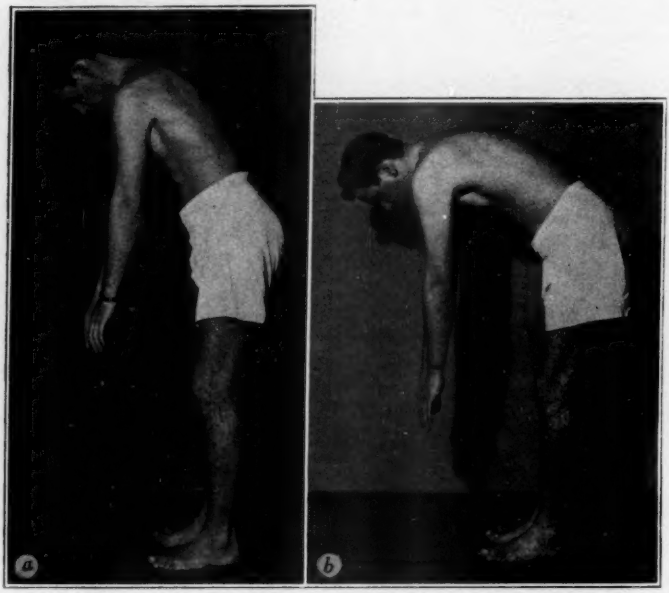

Fig. 10 (case 17).—(*a*) Amount of forward bending of the back and hips possible before ACTH was given; (*b*) after eleven days of use of ACTH.

eyes, anorexia, nausea, vomiting, cramps, mild diarrhea and weakness developed. These lasted four days and were associated with marked diuresis with loss of sodium chloride and dehydration. After a loss of 15 pounds (6.8 Kg.) in three days, the weight became stabilized. Rheumatic symptoms increased slowly thereafter but were not bothersome until May 16, twelve days without ACTH.

Follow-Up.—For three weeks the patient improved, but in August his knees became worse. Between September and October 1949 he improved slightly.

Summary.—ACTH provided marked subjective and objective improvement and a rapid fall of sedimentation rate to normal. A marked increase of 16½ pounds occurred during eleven days of use of ACTH

with slight pretibial edema. When the use of ACTH was discontinued, marked diuresis occurred with dehydration, headache, gastrointestinal symptoms and loss of weight for four days.

CASE 11.—*Moderately severe rheumatoid arthritis; administration of cortisone for eight days, ACTH for twelve days and then cortisone for eighteen days; very marked improvement and prolonged remission*

A woman, 40 years old, had had polyarticular rheumatoid arthritis for five years and eight months, since May 1943. During the first three years the arthritis had been episodic. During an attack in 1945 she was bedridden for nine months. For two years prior to admission to the clinic arthritis had been progressive, despite many remedies, including two courses of gold salts. Her disability interfered seriously with her work as a chemist. For two years she was unable

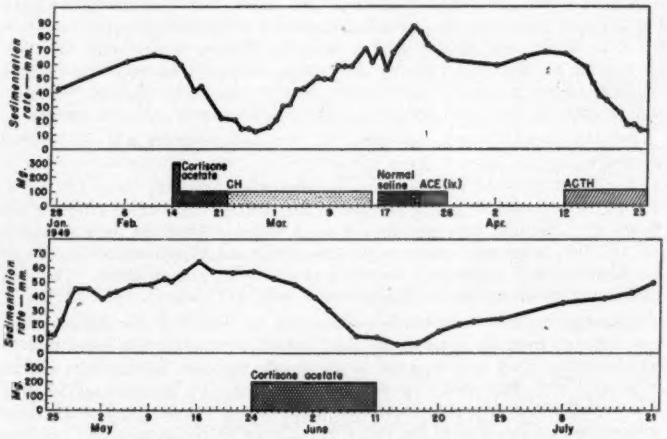

Fig. 11.—Curve of sedimentation rate in case 11.

to lift a glass unless she used both hands. After she awoke it often took her two to four hours to limber up. Tub bathing was difficult; so she usually took shower baths.

She was admitted to the clinic on Jan. 28 and hospitalized on Feb. 5, 1949. Many joints were affected. There was a 45 degree flexion deformity of the right elbow. Wrists, ankles and metatarsophalangeal joints were swollen grade 2 and tender grade 3. Small red scaly lichenified plaques of neurodermatitis had been present one year about each malleolus. Epitrochlear, cervical and axillary lymph nodes were enlarged.

Sedimentation rates increased from 42 to 64 mm. (January 28 to February 14). Roentgenograms showed destructive changes of the right hand and wrist and temporomandibular joints.

Cortisone.—First Course: Cortisone acetate was given for eight days (February 14 to 21): 300 mg. the first day, then 100 mg. daily; total 1 Gm. in eight days (fig. 11). Seven hours after her initial dose she had improved

markedly, a striking sense of well-being developed and most of her stiffness and soreness disappeared. During the next six days (February 16 to 20) muscular and articular stiffness, articular tenderness and pain of joints on walking or at rest disappeared completely. Swellings of wrists and elbows were decreased. The flexion deformity of the right elbow and the neurodermatitis disappeared. Lymph nodes were no longer palpable. Her appetite was improved.

She could get into and out of the bath tub, wash the tub, comb her hair, walk on tiptoes in her bare feet. She stated: "Until recently my judgment and decisions were slow. I couldn't concentrate, think coherently, remember well or follow long conversations. Now I feel normal." She was "too excited to sleep" more than three or four hours some nights but was not tired in the morning. Remission was practically complete.

The sedimentation rate decreased 43 mm. in seven days: from 64 to 21 mm. (February 14 to 20) and was 12 mm. on February 26.

Use of Control Material.—Cholesterol was given daily for twenty-one days. For the first four days the remission continued. The sedimentation rate continued to fall and was 12 mm. on February 26. Then symptoms began to return slowly; the sedimentation rate rose to 70 mm. on March 14, at which time the condition of her wrists and ankles had relapsed completely, although her jaws and metatarsals were still improved. The neurodermatitis did not reappear.

Adrenal cortex extract was given for six days. Results will be reported elsewhere.

Use of ACTH.—ACTH was given intramuscularly: 105 mg. daily (35 mg. at 8 a. m., 4 p. m. and 10 p. m.) for twelve days (April 12 to 23). Within a few hours after the first injection she felt much better. After ten days of use of ACTH, her joints and muscles were subjectively and objectively normal except for slight residual swelling or thickening of the wrists and an elbow. The sedimentation rate fell rapidly, 54 mm. in twelve days, to 12 mm. on April 23.

Although the patient did not know what she was receiving, she guessed that it was different from the material she had received previously. She stated that the antirheumatic effect was as great as previously but that her appetite was not stimulated and she had no "mental lift" ("no sense of happiness as before"). She experienced a generalized headache, slight nausea and mild abdominal cramps within the first two days of use of ACTH; thereafter she noted some "heaviness in the head," dizziness, restlessness, insomnia, fatigue, weakness and listlessness. Because of the latter she was content to rest in her room and did not engage in the demonstrativeness and activity associated with the relief given by cortisone.

Withdrawal of ACTH.—After use of ACTH was discontinued on April 23, the sedimentation rate remained low (12 mm.) for two days, then rose at first rapidly and then slowly to 64 mm. on May 16. Two days after use of ACTH was stopped, rheumatic symptoms began to recur mildly but the fatigue, listlessness and weakness experienced on ACTH disappeared. After four days of increasing rheumatic symptoms, joints improved again and for about two weeks (April 30 to May 14) she felt "fine."

Then some symptoms returned. Walking was painful, and stiffness was considerable. But there was no pain at rest, and the appetite was still good. The patient estimated that "about 30 per cent" of her rheumatic symptoms had returned.

Cortisone.—Second Course: To study the clinical and metabolic effects of larger doses of cortisone acetate, the patient was given 200 mg. (100 mg. twice a day) for eighteen days (May 24 to June 10). Improvement was slight until the fourth day, when she awoke to find most of her symptoms gone again. "I can do any-

thing without thinking of my joints." Again there was a sense of well-being; she was "happy like I was during the first treatment." The appetite was increased, but she was not ravenous. "I'm happy and want to sing." By June 6 after two weeks' use of cortisone there was no tenderness or pain in any joints, even on very firm pressure or forced motion. There was slight swelling or thickening (grade 1) only in the wrists, certain finger joints and the ankles. The patient became active and went shopping without tiring.

Withdrawal of Cortisone.—On June 11, the first day without cortisone, the patient was still euphoric and "explosive"; she laughed and was constantly active. Despite some insomnia and only five hours of sleep, she woke rested.

During this course of cortisone the sedimentation rate fell from 57 to 12 mm. (May 24 to June 8) and continued to fall even after use of cortisone was stopped. It was 7 and 8 mm. on June 14 and 16. Then it began to rise again but more slowly than after previous courses. The patient remained free of symptoms for at least twenty days and almost free for many weeks more. After she was removed from the Metabolism Unit and allowed to eat at will, she ate double servings. The restlessness and excitement gradually diminished.

She was dismissed from the hospital July 21 but remained in town. During August she walked an average of 2 miles a day without trouble except occasional slight fatigue. Some stiffness developed; the appetite began to diminish, and by August 22 slight tenderness developed in a few joints, but others were painless. She was dismissed September 23, after fifteen weeks without cortisone, with an estimated "10 per cent return of arthritis."

Follow-Up.—Although the patient had some weakness and depression, she had little arthritis ("no more than 5 per cent") until Jan. 10, 1950, when her ankles swelled. Within a week she regained 60 per cent of her disability.

Summary.—This patient lost practically all symptoms of her rather severe rheumatoid arthritis during an eight day course of cortisone, maintained her relief only four days thereafter and then had a slow relapse of about 90 per cent within seven weeks. She again became free of symptoms during a twelve day course of ACTH, after which she had a short relapse and then regained her improvement for two weeks. All symptoms again disappeared during a second course of cortisone (eighteen days of 200 mg. daily), after which she maintained her improvement completely for at least three weeks and almost completely for about six months more.

During use of ACTH she had a few mild side effects for a few days but practically none from cortisone. No acne, edema, rounding of the face or hirsutism developed. Enlarged lymph nodes became nonpalpable. Neurodermatitis which had been present for one year about each ankle disappeared during the first course of cortisone and did not reappear.

CASE 6.—*Severe rheumatoid arthritis; administration of compound A, cortisone, ACTH, compound F and cortisone acetate*

A 49 year old woman had severe polyarthritis of three years' duration. Practically all joints but those of the spine were swollen and tender. Both knees were involved by flexion deformities of three months' duration; these varied from 15 to 20 degrees in the right knee to 10 degrees in the left. Her knees were so

stiff and sore that on rising she held onto chairs or the bed for awhile until she could straighten and loosen the knees. She walked with difficulty. Many maneuvers, such as wringing out a washcloth or combing her hair, were difficult.

The patient was admitted to the hospital Dec. 30, 1948. Knees and hands were moderately swollen and markedly painful on pressure or forced motion. Roentgenograms showed destructive changes of knees, wrists, fingers and feet. Sedimentation rates were 40 and 47 mm.

Use of Compound A.—11-Dehydrocorticosterone (Kendall's compound A) was given for seven days, 100 mg. daily (January 3 to 9) (fig. 12). Neither the arthritis nor the sedimentation rate was affected significantly.

Cortisone.—Cortisone (not the acetate) was given for ten days, 100 mg. daily (January 10 to 19). Although the patient did not know that the material had

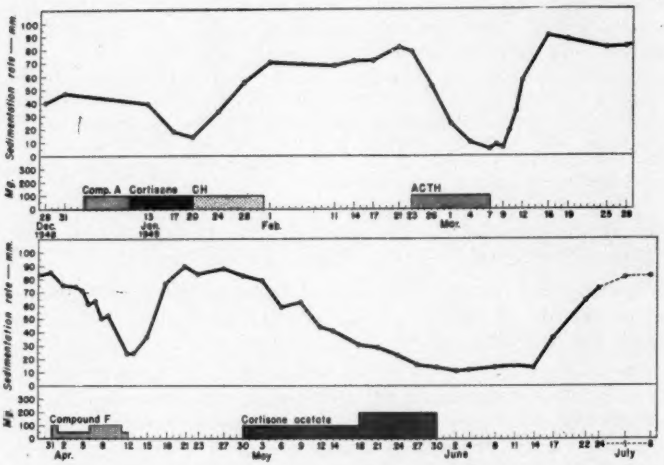

Fig. 12.—Curve of sedimentation rate in case 6.

been changed, she noted a prompt effect; on January 11 it was easier for her to get out of bed and she said "This is the best day I've had in a year." After a week all affected joints had improved. She could bathe without help and comb her hair easily. Flexion contractures of the knees almost disappeared. Muscular stiffness had disappeared; tenderness and swelling disappeared from several joints and lessened in others. She lost within ten days 75 per cent of her symptoms. The sedimentation rate fell from about 40 to 14 mm. (January 20).

Use of Control Material.—Cholesterol was given for eleven days (January 20 to 30). There was a slow relapse for about two weeks and then a flare-up in several joints. In February the patient could walk only a few steps daily because of pain and flexion deformity of the knees which had recurred.

Use of ACTH.—This hormone was given for twelve days, 100 mg. daily (February 23 to March 6). The patient awoke February 25 with no muscular

stiffness or soreness. During the first five days of use of ACTH there were no side effects, but then heaviness in the chest, restlessness, weakness and fatigue developed. She became very hungry. After nine days of use of ACTH her face became a little puffy. She had an estimated 85 per cent loss of disability. Flexion contraction of the knees disappeared completely. The sedimentation rate had fallen precipitously, 73 mm. in twelve days: from 78 to 5 mm. (February 23 to March 6).

Withdrawal of ACTH.—For ten days after use of ACTH was stopped, the patient retained most of her improvement; then there was a relapse, and by March 30 she was as bad as before use of ACTH. The right knee was flexed 20 degrees; the left, 10 degrees. She "hated to see food." The sedimentation rate rose rapidly and was 90 mm. on March 16.

Use of Compound F.—The adrenal cortex hormone 17-hydroxycorticosterone (compound F) was given intramuscularly for twelve days (March 31 to April 11). Our supply of compound F, not the acetate, was extremely limited, just enough for a short term test on 1 patient. We gave 100 mg. the first day, then 50 mg. (25 mg. twice a day) for five days, 100 mg. for five days and 50 mg. for one day. Although the sedimentation rate began to fall promptly, clinical improvement was so slight that on April 6 the dose was doubled to 100 mg. daily for five days. Improvement increased. Slight facial edema was noted for a few days. On April 11 only 50 mg. was given, since our supply was exhausted. The patient lost about 60 per cent of her symptoms while receiving compound F. Flexion contraction of the knees almost disappeared. The sedimentation rate fell 61 mm. in twelve days: from 85 to 24 mm. (March 31 to April 11).

Withdrawal of Compound F.—Within two days symptoms began to increase slowly. The sedimentation rate rose to 89 mm. within nine days. On April 30 a practically complete relapse had occurred.

Use of Cortisone Acetate.—This was given for thirty days: 100 mg. daily for eighteen days (April 30 to May 17), then 200 mg. daily for twelve days (May 18 to 29). On the 100 mg. doses (50 mg. twice a day) the sedimentation rate fell 52 mm. (from 82 to 30 mm.) in eighteen days, but clinical improvement was moderate. The dose was increased to 200 mg. daily (100 mg. twice a day). The patient then improved faster so far as muscles and joints were concerned but she became more tired and sleepy and was content to remain in her room. Rounding of the face was present for a few days. The sedimentation rate became normal, 14 mm. on May 30. The over-all relief was estimated at about 75 per cent.

Withdrawal of Cortisone Acetate.—The patient retained her clinical and laboratory improvement longer than previously. The sedimentation rate remained normal fifteen days, but the lassitude and fatigue that she had while receiving 200 mg. of cortisone acetate daily disappeared. About June 14, two weeks after use of cortisone was discontinued, the sedimentation rate began to rise quickly and symptoms increased. On June 28 she again needed help to rise from a chair; she held onto a chair when walking. For three weeks she was tired and drowsy again. On dismissal, July 29, she estimated that she had retained a slight improvement, perhaps 15 per cent.

Follow-Up.—Since dismissal, the patient's joints have not changed much. Flexion deformities returned mildly. Posthormonal weakness, which began five weeks after use of cortisone acetate had been stopped, lasted three weeks and then disappeared.

Summary.—This patient obtained no relief from compound A, 60 per cent relief from compound F, 75 per cent relief from cortisone and cortisone acetate and about 85 per cent relief from ACTH. Her clinical response to ACTH was better than to cortisone, cortisone acetate or compound F.

Flexion deformities of knees disappeared or almost disappeared during administration of each hormone (except compound A). Sedimentation rates became normal during use of cortisone, cortisone acetate and ACTH and nearly normal during use of compound F; they were not affected by compound A. The rate remained normal longer after the daily use of 200 mg. of cortisone acetate than after use of the other agents.

Only slight signs of hormonal excess developed transiently: none during use of cortisone and slight rounding of the face, fatigue and lassitude during use of cortisone acetate (in 200 mg. doses). Heaviness in the chest, some weakness and fatigue, mild restlessness, mild abdominal gas and cramps developed during use of ACTH but not during daily use of 100 mg. of cortisone or of cortisone acetate. There was no acne, striae or hirsutism. The systolic blood pressure increased 20 to 35 mm. during use of ACTH and about 10 mm. during use of large doses of cortisone acetate; it did not increase during use of 100 mg. of cortisone, cortisone acetate or compound F. When increased, systolic pressures subsided at once when use of the hormones was discontinued. Diastolic pressures were not increased.

During the periods without hormones the patient's temperature was often 99 F., occasionally 99.5 and once 100. It was normal during the use of cortisone, cortisone acetate and ACTH; it was occasionally 99 F. during use of compounds A and F.

CASE 21.—*Severe rheumatoid arthritis very markedly relieved by cortisone*

The patient, a 30 year old woman, was admitted to the hospital June 28, 1949. Arthritis, which began in March 1944, had progressively involved most of her peripheral joints. She became pregnant in November 1947 and after two or three months was almost free of symptoms. Two weeks post partum she had mild rheumatic symptoms which disappeared in two weeks but returned six months post partum and progressed thereafter. It took her two or three hours to limber up in the morning. She slept poorly. Many joints were painful, tender and swollen. The elbows were flexed: the right 30 degrees, the left, 40. Roentgenograms of the right hand revealed pronounced destructive changes.

Sedimentation rates were as follows: 47 mm. on June 13, 102 mm. on June 30, 82 to 88 mm. during July and 88 mm. on July 27.

Effect of Cortisone.—Cortisone acetate was given, 100 mg. daily for fifty-six days (July 26 to September 19). On July 28 the patient woke without the usual morning stiffness and got right out of bed; she stated that she felt as she did when pregnant. By the seventh day soreness and tenderness of joints were

diminishing. She "felt good" but was not euphoric. Her appetite was good, but she was not ravenous. After another week of use of cortisone she pushed a baby buggy and child about a mile; her feet were "slightly tender for five or ten minutes."

After twenty-five days of use of cortisone, slight fulness of the face was present. She then had received the optimal relief; all stiffness and almost all swelling and tenderness had disappeared. The sedimentation rate had fallen 81 mm. in twenty-one days: from 88 to 7 mm. (July 27 to August 16) and was normal. Injections were continued for another month to study the effects on pituitary and ovarian function. There was a continuation but little enhancement of the excellent antirheumatic response of the first three weeks. The sedimentation rate remained normal for thirty-four days. On September 19, the last day on which cortisone was given, the over-all relief was estimated at 90 per cent, the only residues being transient aching of a foot after walking, mild tenderness of metatarsals and slight puffiness of the left knee and fingers. Swelling, tenderness and pain on forced motion had disappeared from other joints. Neither blood pressure nor growth of hair was increased. Cortisone exerted no demonstrable effect on production of gonadotropin or estrogen. Menses occurred regularly.

Use of Control Material.—Cholesterol was given for ten days (September 20 to 29). For two days the sedimentation rate remained normal and there was no increase of symptoms. On the third day without cortisone the right ankle became slightly sore. When three days later the patient's hands became slightly stiff and sore, she became worried and, without our knowledge, she had her husband come to her room to watch the injections to see whether they were different. He thought that they were not, but despite this she told him that they must be different. At the time of her dismissal, after eleven days without cortisone, she retained about 70 per cent of her improvement.

Follow-Up.—Within a month, most of the previous disability returned. Moderate to marked posthormonal weakness and lassitude developed for four to six weeks. Thereafter the patient improved somewhat. Menses continued normally.

Summary.—The antirheumatic response was about 90 per cent. The sedimentation rate decreased rapidly to normal and remained normal for thirty-four more days, as long as use of cortisone was continued. Slight fulness of the face developed after twenty-five days of use of cortisone.

CASE 23.—*Very severe subacute rheumatoid arthritis; marked to very marked effect from cortisone*

A girl, 17 years old, was admitted to the hospital July 25, 1949 with severe subacute polyarthritis of five months' duration. In February her metatarsals became painful. In April practically all joints of the extremities were affected. She was first brought to the clinic May 27. It was difficult for her to use a pen, open a milk bottle, hold a glass or walk. Of many affected joints, swelling and tenderness were greatest in hands and feet. Temperatures were 99 to 101 F. She had not menstruated since late in March. The sedimentation rate was 77 mm. Roentgenograms of several joints revealed only periarticular swelling. Symptomatic treatment for two weeks gave little relief.

The patient was readmitted to the hospital on July 25. She could walk only a few steps with assistance. Slight flexion deformities of the elbows and knees were present. Fingers, wrists and knees were painful. Flexion deformity of

the elbows had increased to 30 degrees on the right and 25 on the left. The knees were tender. Mild fever (temperature of 99 to 100.5 F.) was present. On her forehead was mild acne which had been present on and off for three years. The sedimentation rate was 78 mm. (July 26). Between August 4 and September 7 three steroids were given; results will be reported later. The patient was almost helpless in bed. All she could do for herself was to pull up the sheets to cover herself.

Use of Cortisone Acetate.—This was given for thirty-eight days (September 15 to October 22): 300 mg. the first day and 100 mg. once daily thereafter (fig. 13). On the second day the appetite improved notably. The patient could straighten her elbows and knees each about 10 degrees more than a few days previously. On the third day, after a good night's sleep, she turned over several times, sat

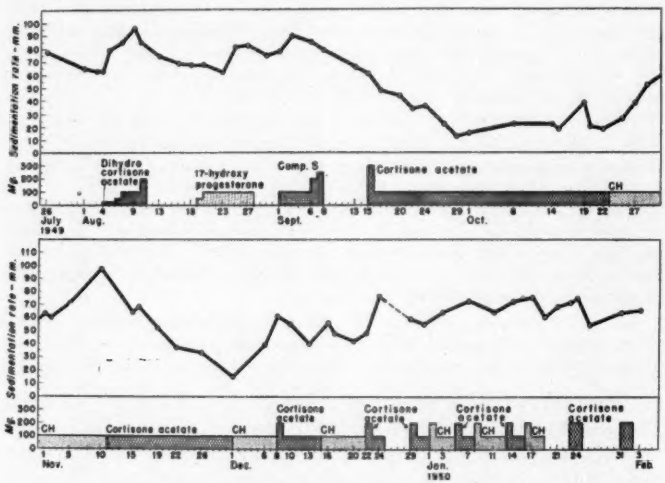

Fig. 13.—Curve of sedimentation rate in case 23.

up in bed unassisted, noted much less stiffness and pain and could make fists for the first time in four months. That day she was so hungry that she ate hamburgers and malted milk between meals. That night she "slept and slept and slept." On the fifth day her parents, who had not seen her for about a week, visited her and became emotional in view of the girl's improvement. Pain at rest had disappeared; swelling, tenderness and stiffness were decreased. For the first time in over seven weeks she fed herself. The next night she was restless; she could not sleep, not because of pain but because she was "excited." She was up in a wheel chair for one and a half hours on the eleventh day and for three and a half hours the next day.

After two weeks of taking cortisone the sedimention rate was normal: 13 mm. (September 29). All joints were improved but the flexion contractures of the knees were somewhat refractory. The right one, previously flexed 60 degrees, was now flexed 40; the left one, previously flexed 70 degrees, was now flexed 25. It was estimated that her arthritis had subsided 75 per cent.

To hasten straightening of the patient's knees, sandbags were now placed on her thighs above her knees for about two to three hours daily and aluminum night splints and physical therapy were used. On October 2 small reddish striae were noted over the hips. On October 6, after three weeks of use of cortisone, she was able to walk a little around the room, holding onto and pushing a chair ahead of her. But improvement in the knees was slow; on October 13 the right knee was flexed 20 degrees and the left 10. The flexion deformities of the elbows had disappeared. Rounding of the face was now slight but definite. The acne, which was present before cortisone was given, had not increased. There was no edema or hirsutism. After seven weeks of use of cortisone all joints except the knees were normal even on forced motion. The knees were still slightly tender, swollen and flexed: the right 10 to 15 degrees; the left, 5. The sedimentation rate was 18 mm. on October 22. Although the patient walked about 30 feet (9 meters) each day holding onto something and was active in bed, we could not get her to attempt more walking.

Use of Control Material.—Cholesterol was given daily for nineteen days (October 23 to November 10). About thirty-six hours after use of cortisone was discontinued slight stiffness returned. Symptoms then increased. Slight fever returned. The patient lost her appetite and was emotionally upset by the return of arthritis. During this time she had about a 60 per cent relapse. She was unable to walk. The sedimentation rate rose rapidly from 18 to 97 mm. (October 22 to November 10).

Cortisone.—Second Course: Cortisone, 100 mg., was given once daily for twenty days (November 11 to 30). Within twelve hours of the first dose improvement began. On the fifth day, with someone walking beside her she walked about 100 feet (30 meters). After two weeks she felt better than at any time during the previous course of cortisone. On November 28 (eighteen days of use of cortisone) she went downtown with her parents for dinner and walked unassisted three or four blocks without reaction. The only residues were slight thickening and tenderness of the wrists and knees and residual flexion of 10 to 15 degrees of the knees. The over-all relief was about 90 per cent. Again the sedimentation rate fell rapidly to normal. Acne had disappeared, but the face was rounded and the striae on the thighs, though no more numerous, were perhaps more deeply colored and a little broader.

Interrupted Use of Cortisone.—Third Course: To determine whether equal or better and more lasting clinical results with full tolerance of cortisone could be obtained thereby, it was decided to give cortisone for short interrupted periods, of two to seven days each, with interludes of four to seven days with or without cholesterol.

Although the antirheumatic effect was satisfactory each time cortisone was given, repeated administrations in this manner made no appreciable difference in the duration of the remissions resulting therefrom. The patient was dismissed February 24.

Summary.—This patient responded well to these two courses of cortisone, of thirty-eight and twenty days respectively, lost from 75 to 90 per cent of her disability, regained a normal sedimentation rate, lost flexion deformities of the elbows and retained only slight residual flexion deformities of the knees. During a third course of interrupted

dosage, the antirheumatic effect was generally present only on the days when cortisone was given. Some rounding of the face and gluteal striations developed.

CASE 4.—*Moderately severe rheumatoid arthritis; marked effect of cortisone; three courses*

A physician, 41 years old, was seen at the clinic many times because of various illnesses. These included recurrent gastrointestinal disturbances, diagnosed as postcholecystectomy syndrome. His rheumatic disease was episodic between 1935 and 1946. After February 1947 the fibrositic element was chronic. Short articular flare-ups, lasting one or two days, came every few days. In 1948, despite many remedies, rheumatoid arthritis remained active.

He was admitted to the hospital Oct. 22, 1948. He had difficulty in shaving, dressing and walking. Various joints were moderately or markedly tender and swollen. Between October 22 and November 3, sedimentation rates varied from 25 to 50 mm.

Effect of Cortisone.—First Course: Cortisone (not the acetate) was given, 50 mg. twice daily for twelve days (November 3 to 14). No significant change was noted the first thirty hours, but on the afternoon of the second day muscles were less painful. The next morning the patient awoke feeling much better. His stiffness was almost gone. He got up and shaved easily and at once, the first time in six weeks. He was ravenous. That afternoon he walked normally for the first time in months. During the next two days most of his stiffness disappeared and swellings receded.

During the next few days symptoms and sedimentation rate increased in this patient (and in 2 other patients at the same time) from the use of one of our early unstable suspensions. With use of a new preparation the patient's flare-ups subsided, the sedimentation rate decreased and by November 11, the ninth day of use of cortisone, symptoms were notably less. He became active mentally and in one week finished writing two papers that he had not had the energy to finish previously. He was free of symptoms, but minimal swelling and tenderness of a few joints were still present. The sedimentation rate fell to 24 mm. (November 15) and was normal, 16 mm., four days after use of cortisone was stopped (November 18). The over-all relief was 85 per cent.

First Withdrawal of Cortisone.—Optimal relief was maintained only four days; then symptoms returned. Within seven weeks the sedimentation rate rose to 43 mm. The patient was so uncomfortable that he reentered the hospital on Christmas Day.

Effect of Cortisone.—Second Course: Cortisone or cortisone acetate was given daily between Dec. 30, 1948, and Feb. 6, 1949, except for three days. Cortisone, 100 mg., was given for four days; 125 mg., for one day; 150 mg., for three days; none, January 7 to 9, and 100 mg., for sixteen days. Cortisone acetate, 200 mg., was given on January 26; 100 mg., for the next 11 days.

Again no improvement was noted for about thirty hours. The second day began as a "very bad day." The patient was weak and could not wash or shave. In the afternoon he began to improve and felt so good that he went to a New Year's Eve party. He sat in conversation for two or three hours without becoming stiff.

He woke up New Year's morning almost free of stiffness and so hungry that right after his hospital breakfast he crossed the street to a restaurant and had

more coffee and toast. By afternoon subjective symptoms had almost disappeared. Objective signs of articular swelling and tenderness were lessened. The sedimentation rate became normal: 11 mm. on January 5. On January 2 a mild epidemic gastrointestinal upset developed and lasted for thirty-six hours. On January 7 a different type of gastrointestinal disturbance, reminiscent of those he often had had in previous years, developed: epigastric "throbbing" and tenderness with occipital headache. Although cortisone did not seem to be responsible, its use was discontinued for three days (January 7 to 9), during which time rheumatic symptoms quickly increased and the sedimentation rate rose to 25 mm. (January 9).

Daily doses of 100 mg. were begun again. After six days the patient went to a dance for the first time in six months. For three more days he had "no arthritis" and worked in his office. Sedimentation rates remained slightly above normal: 21 to 25 mm.

On January 26 cortisone was replaced by cortisone acetate; 200 mg. was given the first day and then 100 mg. daily for eleven days. The sedimentation rate became normal and remained normal (14 and 15 mm.). The patient came to the hospital each morning for his daily injection, then worked all day at his office and spent about two hours each evening with his children.

Use of Control Material.—The patient had previously agreed to trial with a control material, the substitution to be made without his knowledge. Cortisone acetate was replaced by cholesterol, which was given for five days (February 7 to 11). On February 7 and 8, he worked full time, although symptoms promptly increased. The next day he could not shave. He quit work at noon and was unable to work the rest of that week. He told one of us, "I don't know what I'm getting, compound E or the control material, but if I'm getting the former, it's no good!" The sedimentation rate rose to 55 mm. February 24.

Cortisone.—Third Course: Cortisone acetate was given on sixty-one of the seventy-one days from February 25 to May 6; the three brief interruptions were for two to four days each. It was given thus: 100 mg. daily for thirty-seven days, through April 2; 200 mg. on April 7; 100 mg. daily for three more days; none for four days; 100 mg. daily for fifteen days (April 15 to 29); a two day interruption, then 200 mg. daily for four days, and 100 mg. on the last day (May 2 to 6).

The effect was similar to that of the first two courses. On February 26 the patient woke "without toxicity and with half of the fibrositis gone." He soon went to another dance, without aggravation of the symptoms. Most of the time he was almost, but never entirely, free of rheumatic activity. A reserve naval officer, he went on a two weeks' naval inspection trip, taking his own injection of cortisone intermittently (hence the brief interruptions). He walked a great deal, climbed many stairs and ladders. Mild flare-ups occurred, but generally he felt stronger, slept better and had no toxic effect. Two days after his return (April 3) thrombophlebitis of the left short saphenous vein developed for about five days in conjunction with a moderate rheumatic flare-up. The daily dose of cortisone acetate was increased to 200 mg. The sedimentation rate rose during this phlebitis, from 22 to 57 mm. (April 29-May 5).

Third Withdrawal of Cortisone.—Within three days the patient felt weak and was depressed and rheumatic "without capacity to initiate anything." Post-hormonal weakness and feeling of depression cleared in one month. Discouraged because his arthritis relapsed even after the third course, he elected to try chrysotherapy, which was begun in June.

Summary.—This patient's moderately severe, unusually painful rheumatoid arthritis responded well but never completely to each of three courses of cortisone. His over-all relief varied between 85 and 95 per cent. Sedimentation rates became normal. But even when he was practically free of symptoms, minimal tenderness and swelling were usually present somewhere. Being a physician, the patient summarized the effect of cortisone on himself thus: "All the disabling part of my disease is gone. The little articular flares are a nuisance but to me unimportant, much less important than the stiffness, which is practically gone. and the toxicity of the disease, which to me is the worst feature of all. It is the toxicity that prevents me from working and makes me so miserable. That is gone, and I'm a functioning individual again. All I have left is arthritis in miniature."

In the second and third courses the patient noted a decrease in libido but not potentia. No acne, edema, hirsutism or increased blood pressure developed, but after the third course he noted muscular weakness for about a month. The arthritis promptly returned after each of three courses of cortisone.

CASE 2.—*Severe rheumatoid arthritis and rheumatoid spondylitis; marked response to cortisone given almost continuously for two hundred and fifteen days*

A 41 year old owner of tourist cabins had his first transient symptoms of spondylitis in 1936. Episodic arthritis of peripheral joints began in 1943. After 1944 both conditions were chronic. For a year prior to admission he was unable to work and required help to dress and to get out of bed.

He was admitted to the hospital Sept. 5, 1948. Many peripheral joints were swollen and tender. Present were flattening of the lumbar region of the spine, dorsal kyphosis and marked limitation of motion of the entire spine. The right knee was flexed 10 degrees. The left arm could be abducted only 15 degrees. Roentgenograms of the spine revealed marked destruction of the sacroiliac joints and early calcific changes in lumbar ligaments. The sedimentation rate was 122 mm. on September 3.

Various treatments were ineffective. The sedimentation rate remained high: 127 mm. on September 20 and 118 mm. on October 5. Three days prior to the use of cortisone, acetylsalicylic acid was withdrawn and the patient was more uncomfortable than before. On October 5 many joints were swollen and tender.

Effect of Cortisone. First Course: Cortisone (not the acetate), 100 mg., was given daily for seventy-five days (October 5 to December 18) (fig. 14). Four hours after the first injection the patient woke from an afternoon nap "normally without being wakened by pain." He felt relaxed. Although a stoical person he was emotionally stirred by the day's experience. Within two days he lost much stiffness. Thereafter, improvement was slow and steady. By October 15 arthritic activity was minimal. He walked about the halls and climbed stairs. The sedimentation rate was falling slowly; it was 97 mm. on October 15.

Beginning October 21 the suspension of cortisone given to him contained crystals larger than those previously used. Because of their poorer absorption he had a mild articular flare-up for a few days; the sedimentation rate rose slightly.

A new suspension of cortisone was prepared; improvement recurred. The sedimentation rate fell to 66 mm. on November 16, at which time (after six weeks of use of cortisone) swelling and pain at rest had disappeared from all joints except the right knee. About November 11 the patient noted transient mild dizziness, increased energy and restlessness. One day he walked sixteen blocks and climbed eight flights of steps without articular irritation. Prior to this his weight had

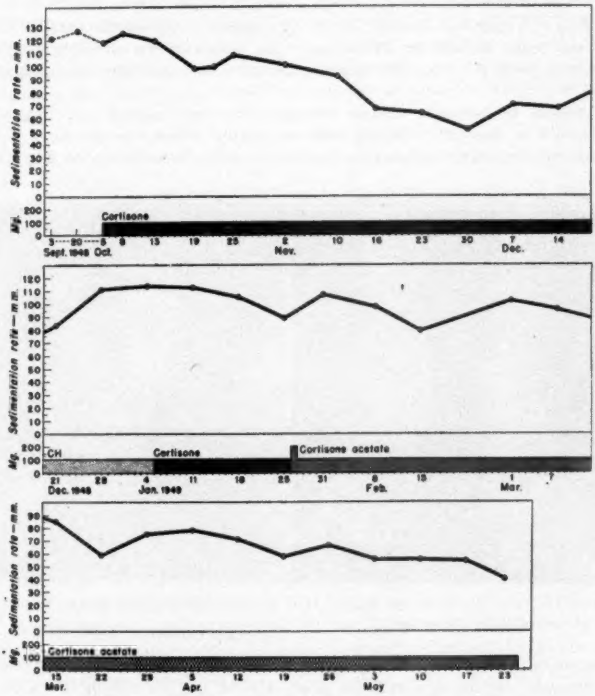

Fig. 14.—Curve of sedimentation rate in case 2.

been relatively constant, varying between 143 and 146 pounds (64.9 and 66.2 Kg.). He then gained weight to 165 pounds (74.8 Kg.) by December 17. Dizziness disappeared on November 27. By December 10 the patient felt better than at any time for three months. His joints continued to give minimal trouble. The estimated arthritic remission was about 80 to 90 per cent.

Despite the continuing excellent condition of the patient's joints, the sedimentation rate remained relatively refractory. Although it had fallen steadily from 125 to 50 mm. (October 8 to November 30), it then rose slowly to 66 mm. on December 14.

Use of Control Material.—Without the knowledge of the patient or the three clinical authors, cholesterol was given for seventeen days (December 19 to January 4). Although the sedimentation rate rose rather quickly, his joints remained unchanged for about ten days, but after one day without cortisone he began to lose appetite and energy and muscular stiffness developed. The three clinical observers promptly recorded their belief that a change from cortisone to cholesterol had been made on or about December 20. Actually the change had been made December 19.

Effect of Cortisone.—Second Course: On January 5 the second course of cortisone was begun without the knowledge of the patient or the attending clinicians, but within thirty-six hours the response indicated that cortisone was being given again.

Cortisone or cortisone acetate was given for one hundred and forty days (January 5 to May 25): 100 mg. daily except for 200 mg. on one day. Within a week the joints were as free of symptoms as at any time during the first course

Fig. 15 (case 2).—Feet and ankles; (*a*) before cortisone was given; (*b*) reduction of swelling by cortisone.

of cortisone. After the patient had received it sixteen days, the only evidence of rheumatic activity was stiffness grade 1— of the left shoulder, fingers and neck and persistent moderate swelling of a painless right knee. Even the stiff left shoulder could now be abducted 90 to 100 degrees. But as before, the sedimentation rate was relatively refractory (much more so in this case than in any other) and fell slowly from 115 to 89 mm. (January 4 to 25).

About January 20, after two weeks of use of cortisone, the patient first had trouble in focusing his eyes for reading. By February 8 his remission was again about 90 per cent. On and after January 26, cortisone was replaced by cortisone acetate (fig. 15).

For years the patient had thought that he had "sinus trouble," as evidenced by postnasal drip. In February 1949 foul pus was aspirated from the maxillary sinuses.

For weeks we had been puzzled by the persistent refractoriness of the sedimentation rate despite the almost complete arthritic remission. We were interested to see whether treatment of an infected focus, the sinusitis, might influence

the refractory synovitis and sedimentation rate. The latter was still elevated: 79 mm. on February 15. Submucous resection, formation of antral windows and ethmoidectomy performed on February 18 did not influence the rate materially; it gradually rose to 102 mm. on March 1, then slowly fell to 59 mm. on March 22. Nor did this procedure influence the mild residual swelling of the right knee.

On March 24, after eleven weeks of the second course of cortisone and after receiving the hormone daily for one hundred and fifty-three out of the previous one hundred and seventy days, the patient stated, "I can walk as far or as long as I like, but I can't hurry." He walked 2 to 5 miles (5 to 8 kilometers) a day.

Use of cortisone was continued until his dismissal on May 25, at which time the sedimentation rate was at its lowest value, 40 mm. The only residues were mild thickening of the right knee and moderate limitation of motility of the left shoulder and spine. The patient was asymptomatic. Flexion deformity of a knee and elbow had disappeared. His weight was 184 pounds (83.5 Kg.), a gain of 41 pounds (18.6 Kg.) since admission. He had a paunch and his face was fleshier—nutritional effects.

Side Effects.—During these months of use of cortisone minimal side effects developed as follows: In the first course of cortisone after a month there were mild transient dizziness, increased energy and restlessness. Then these symptoms apparently disappeared. After about two weeks of the second course of cortisone, the patient noted some difficulty in focusing his eyes when reading. This was also of short duration. After refraction, presbyopia was corrected by glasses and his eyesight improved. No increased growth of hair was noted during the first course, nor did he have to shave oftener during the second course, but he thought that his hair grew faster and during this course he had more frequent hair cuts. No acne, edema, moon face or increased blood pressure occurred.

Follow-Up.—In June, about two weeks after the patient's dismissal, the condition of right knee flared up moderately; other joints were unchanged. Then arthritic activity increased slightly. Moderate exhaustion occurred for three or four weeks. Late in August (three months without cortisone) he visited the clinic. He thought that he had lost 15 to 20 per cent of his maximal improvement. The right knee was moderately swollen and slightly tender.

Summary.—This patient's severe rheumatoid arthritis and spondylitis were relieved almost completely during two courses of cortisone, the first for seventy-five days and the second for one hundred and forty days with an interval of seventeen days between courses. Flexion deformities of a knee and elbow disappeared. Motion of a badly stiffened shoulder was markedly increased. Despite the excellent antirheumatic effect, the sedimentation rate was unusually refractory but finally decreased to 40 mm. Surgical treatment for severe purulent sinusitis did not enhance the effect of cortisone or affect the joints or the sedimentation rate. The patient tolerated well the prolonged use of cortisone and had only mild transient side effects, which included posthormonal exhaustion.

CASE 3.—*Severe rheumatoid arthritis; marked results from three rather long courses of cortisone; no effect from compound A*

A 64 year old man began to have rheumatoid arthritis episodically in 1938, and it became rather chronic in 1943. In February 1946 his feet were sometimes swollen for weeks. Since May 1948 he had many chronically painful stiff joints.

Crutches were used part of the time for several months before admission; for two months they had been necessary whenever he walked. He had pneumonia in 1933 and a moderately productive cough thereafter. For a month before admission the cough was worse.

The patient was admitted to the hospital Sept. 14, 1948. Most of his peripheral joints were affected. The right elbow was slightly flexed; rheumatoid nodules were present over the elbows and a big toe. The knees were tender and slightly swollen; the left was flexed 5 degrees. The feet were swollen and painful. There was pitting edema grade 2 of the ankles and feet. Roentgenograms of several joints showed osteoporosis only. The sedimentation rates were 56 and 51 mm.

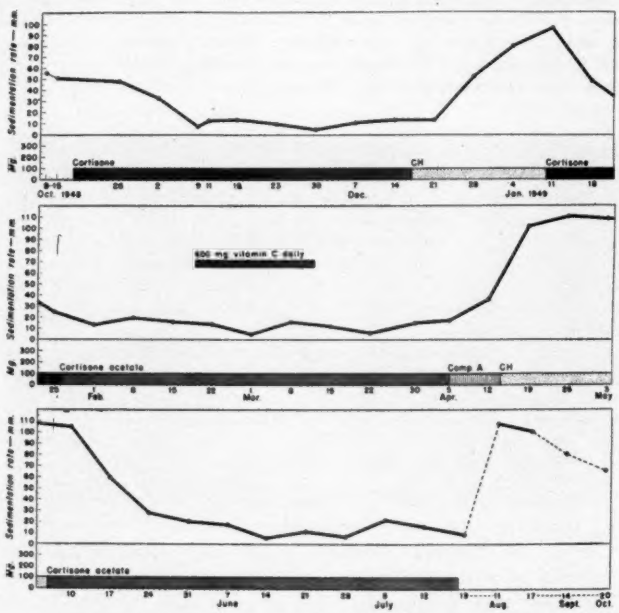

Fig. 16.—Curve of sedimentation rate in case 3.

on October 8 and 15. Notable clubbing of fingers with cyanotic nails was present. Examinations for tuberculosis gave negative results. Roentgenograms revealed bilateral bronchiectasis. The temperature was essentially normal.

Symptomatic treatment for a month had little effect. The patient shuffled along on crutches. He used two hands to lift a book or turn a door knob.

Effect of Cortisone.—First Course: Cortisone (not the acetate) 100 mg. (50 mg. twice a day) was given for sixty days (October 18 to December 16) (fig. 16). After one day stiffness decreased and he walked about 90 feet (27 meters) without crutches. On the fourth day he had no pain at rest and he walked 150 feet (46 meters) without crutches. On the seventh day swelling of joints was gone and tenderness was much less. The rheumatoid nodule over the

big toe was smaller. The appetite was increasing. The patient discarded his crutches all day, the first time in nearly two months. The sedimentation rate, initially refractory, fell to normal. Gradual improvement with increased energy and marked sense of well-being occurred. After twenty-five days of use of cortisone symptoms and signs were absent in several joints and minimal in the rest. Flexion deformities of the elbows and knees disappeared. The patient walked out of doors, eight blocks without crutches. From November 1 to December 14 the arthritis was almost completely in remission and sedimentation rates remained normal. The patient gained 16½ pounds (7.5 Kg.) (150½ to 167 pounds [68.2 to 75.7 Kg.]) during the course of cortisone administration.

The cough and expectoration from his bronchiectasis decreased, and the clubbed soft tissues adjacent to his curved nails appeared to be reduced in thickness. The patient thought that his skin had become oilier, and it was difficult for him to get a close shave. If he went out anywhere, he shaved twice a day.

Use of Control Material.—On the fourth day he had less energy, poor appetite, transient epigastric pain, diarrhea (for three days), fleeting headache and increased cough. By December 26 many joints had become moderately stiff and slightly tender and painful on forced motion. His skin was drier, and again he shaved once daily. The three clinicians recorded their belief that "on or about December 20" cortisone had been replaced by cholesterol. Actually the replacement was made on December 17, but the clinical and biochemical improvement continued three or four days more (sedimentation rate still normal, 14 mm. on December 21).

Cholesterol was given daily for twenty-four days, during which time the sedimentation rates rapidly rose to 96 mm. Weakness, irritability, poor appetite and "toxicity" returned faster than articular symptoms, but by December 28, after twelve days without cortisone, most of his articular disability had returned. Then pitting edema about the ankles, which had disappeared during use of cortisone, reappeared.

Cortisone.—Second Course: Cortisone was given, 100 mg. daily for sixteen days (January 10 to 25), followed by cortisone acetate, 100 mg. daily for sixty-nine days (January 26 to April 4), a total of eighty-five days. Within three or four days most of the symptoms had disappeared. Sedimentation rates fell 83 mm. to normal values in three weeks and remained so during February and March. The patient's remission was again almost complete. He often walked 1 to 2 miles or more a day without crutches. Earlier his gain in weight had resulted in a paunch; therefore he accepted a diet of 1,500 calories daily. Although he was ravenous, he slowly lost 4 pounds (1.8 Kg.).

There were no disturbing side effects. In February the texture of his hair seemed finer; growth of hair on his face was increased slightly, and edema of ankles again disappeared.

Vitamin C was given, 600 mg. orally daily, for three weeks (February 19 to March 11). It did not appear to enhance or diminish the effect of cortisone.

Effect of Compound A.—This was given for nine days, 100 mg. daily (April 5 to 13). Fatigue, considerable stiffness and minor articular swellings returned. The sedimentation rate rose from 17 to 36 mm. within a week.

Use of Cholesterol.—This was given for twenty-two days (April 14 to May 5). Sedimentation rates increased rapidly. Stiffness, swelling, tenderness, anorexia, weakness and fatigue returned. Slight pretibial edema was present. While receiving cortisone the patient read books on philosophy; now he could not even concentrate on detective stories.

Cortisone.—Third Course: This was given for seventy-three days, 100 mg. daily (May 6 to July 17). The effect was as before. Sedimentation rates fell to normal and again remained normal as long as cortisone was given. For the third time the remission was almost complete; only minimal tenderness of a few joints on heavy pressure remained. Again his cough diminished; his beard thickened. He often walked 2 or 3 miles a day. Using a 1,500 calory diet, he gained 4½ pounds (2.0 Kg.) during these ten weeks. The blood pressure remained normal. The sedimentation rate was 8 mm. on July 18.

Withdrawal of Cortisone.—Use of cortisone was discontinued July 18. The patient retained his improvement ten days, and then symptoms slowly returned. His hair became somewhat thin. The sedimentation rate was 107 mm. on August 11. Dependent edema returned about the ankles. Weakness, fatigue and mental apathy were present. Weakness, which became prominent after cortisone was withdrawn, decreased gradually within three weeks. In August the patient still retained some of his improvement. When he went home, on Oct. 20, 1949, his joints were about as they were in September 1948.

Summary.—This severely disabled patient received cortisone almost continually for nine months (Oct. 18, 1948 to July 17, 1949): that is, on two hundred and eighteen of two hundred and seventy-three consecutive days in three closely spaced courses of sixty, eighty-five and seventy-three days respectively. During each course his arthritis became almost inactive and sedimentation rates became and remained normal. He became able to walk 2 or 3 miles a day without crutches. He tolerated the prolonged use of the hormone with only mild side effects. During the courses his hair and beard thickened; between courses there was transient thinning of hair. Exhaustion and fatigue were present before and between courses. A transient increase of exhaustion after each course may have been hormonally induced.

Dependent edema, which affected the ankles and feet before admission and after the use of cortisone, decreased or disappeared during each course. Symptoms of bronchiectasis improved definitely during each course.

Compound A, given for nine days, had no effect on joints or the sedimentation rate.

GROUP 3: MARKED ANTIRHEUMATIC EFFECT WITH MODERATE SIDE EFFECTS

CASE 15.—*Severe rheumatoid arthritis; very marked results from cortisone and ACTH*

A 29 year old man had mild recurrent lumbar backache in 1945. Polyarthritis began definitely in April 1946. In 1947 he had to quit college because of painful feet. He was admitted to the hospital March 4, 1949. His elbows were slightly swollen, very tender and painful on forced motion (grade 2+ and 3). Flexion deformities were present: right elbow 45 degrees, left elbow 30 degrees and knees 5 degrees. His fingers were swollen, tender and painful (grade 3). His wrists and joints of his lower extremities were slightly swollen, moderately tender

and painful. The spine was slightly stiff from muscular involvement, not spondylitis. Roentgenograms of fingers and the left knee showed early destructive changes. Sedimentation rates were 35, 75 and 11 mm. on Feb. 2, March 5 and March 29, 1949, respectively.

Use of Control Material.—Cholesterol was given daily for six days (March 28 to April 2) without significant effect. Flexion of the knees increased to 20 degrees.

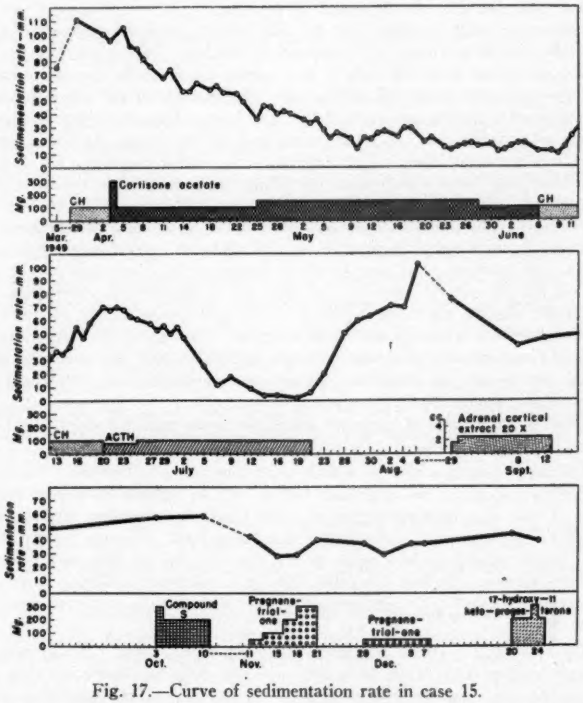

Fig. 17.—Curve of sedimentation rate in case 15.

Effect of Cortisone Acetate.—This was given for sixty-four days (April 3 to June 5): 300 mg. the first day; 100 mg. daily for twenty-one days; 150 mg. daily for thirty-three days and 100 mg. daily for the last nine days (fig. 17).

On the morning of April 3 before the first dose of cortisone was given the patient had to be brought to the conference room in a wheel chair. That afternoon his roommate noted that the patient was walking more rapidly. He had no pain, picked an object off the floor, previously an impossibility, and was so hungry that he was "trying to think up some angles so he could get something extra to eat." That night he slept soundly until 4 a. m., when he woke to find most of his stiffness gone. He became excited and stayed awake thinking and "daydreaming." "I suddenly sat up in bed this morning, pulled up my covers, found myself limber

and decided I could lick this thing [his disease] after all. I started planning for the future." At breakfast he "wolfed" his food and walked to the conference room. Stiffness was markedly reduced.

During the next three weeks on doses of 100 mg. daily he continued to improve. Sedimentation rates fell from 95 to 36 mm. from April 3 to 25. Some days he was practically free of symptoms, "98 per cent well" as he put it. On other days he had mild stiffness, pain and tenderness. Flexion deformities of the elbows had decreased: right, 30 degrees; left, 20 degrees. Those of the knees disappeared. At this point the over-all relief was 90 per cent.

Because of mild residuals and the still slightly elevated sedimentation rate, the daily dose of cortisone was increased to 150 mg. During the first few days on this increased dose the patient was sometimes mentally normal, sometimes stimulated and restless, sometimes sluggish. Occasionally he had transient blurring of vision and a burning sensation of the right knee. Then he adjusted to the new dosage, was cheerful and had a continuing sense of well-being. At first it appeared as if the increased doses would eliminate the minor residues; his symptoms diminished still more. But minor variations continued; some excellent, almost symptomless days and others when this or that joint had a slight flare-up. The over-all average relief remained at about 90 per cent. The sedimentation rate continued its slow fall. It was 14 mm. on May 10, rose 15 mm., then became normal and remained so as long as use of cortisone was continued.

One day the patient went on a picnic with his family and "spent four hours on my feet chasing my young daughter." The next day he mowed the front lawn, and this activity produced only slight stiffness. He was in the hospital but was allowed to spend some time daily with his family, in town. No change in growth of hair and no acne or increased blood pressure were observed. When questioned, he expressed the opinion that he felt less libido.

Prior to withdrawal of cortisone, daily doses were reduced from 150 to 100 mg.

Use of Control Material.—Cholesterol was given for two weeks (June 6 to 19). In five days, symptoms and the sedimentation rate began to increase. His sense of well-being changed to an "unpleasant feeling with an inability to concentrate." By June 11 (six days without cortisone) many joints were swollen, tender and stiff. Flexion contractures of elbows and knees reappeared. Shaving became difficult. The patient stayed in bed most of the time because of pain and exhaustion. Appetite lessened; he lost 7 pounds (3.2 Kg.) in a week. He lost much of his antirheumatic effect. The sedimentation rate rose 60 mm. in eleven days: from 10 to 70 mm.

Effect of ACTH.—This was given thirty-one days: 75 mg. (25 mg. three times a day) for five days (June 20 to 24); 100 mg. daily for twenty-six days (June 25 to July 20). For three days prior to the use of ACTH and during the first day thereafter, he was slightly feverish (temperature 99 to 100 F.). The fever disappeared after twenty hours of use of ACTH. The antirheumatic effect of ACTH began twelve hours after the first injection. Stiffness and aching quickly lessened. Within twelve days the patient was again relieved of almost all his symptoms. Swelling disappeared except for a slight residue (grade 1) in the hands. Tenderness and even pain on forced motion practically disappeared, as did the flexion deformities. The appetite was very good. His improvement was rated 95 per cent. "I feel better than I have since my arthritis began." He noted mental stimulation and was "restless and a little tense." He felt the urge to do many things. He could walk and climb stairs normally, but endurance was low and exhaustion resulted. The blood pressure was not affected. The sedimentation rate fell rapidly and was normal after seventeen days of use of ACTH.

Asthenia was marked during the last few days of use of ACTH and was associated with a reduced serum potassium level. The patient again noticed decreased libido and potentia. But within a week after use of ACTH was discontinued, these were normal.

Withdrawal of ACTH.—Two days after ACTH was withdrawn, there was an exacerbation of the articular condition lasting for three days, after which the patient regained for a few days 80 per cent of his recent improvement. Then most of his rheumatic symptoms gradually returned. The elbows flexed 15 degrees each; the knees, 10 degrees.

Then four related substances were given, results of which will be reported elsewhere.

Summary.—The use of either cortisone or ACTH in this case quickly reduced the polyarthritis from a severe to a very mild degree. Sedimentation rates were quickly reduced from high values to normal and remained normal as long as the hormones were used. But the patient's disease was never entirely controlled, even by doses of 150 mg. of cortisone or 100 mg. of ACTH daily; although he was often practically free of symptoms, minor residues persisted—"arthritis in miniature." If the larger doses of cortisone were more effective than the smaller doses the difference was not great, and mild intolerance to the former developed: mental restlessness and some exhaustion, to which he then seemed to adjust. Libido, decreased during the use of cortisone and ACTH, promptly became normal on withdrawal of the hormones. No acne, edema or rounding of the face occurred. Exhaustion, mild after use of cortisone was discontinued, was more marked during the use of ACTH.

CASE 10.—*Moderately severe rheumatoid arthritis; very marked relief from cortisone*

A clerk 49 years old, was admitted to the hospital Dec. 30, 1948. His arthritis began suddenly August 5. Typing became difficult. Ankles, heels, feet, shoulders and muscles of the thighs became affected. On December 22 his right knee became swollen and painful, and for this reason he quit work.

The patient arrived on crutches, so disabled that he was admitted directly to the hospital. He was big and heavy: 6 feet (183 cm.) tall and weighing 222½ pounds (100.9 Kg.). His wrists were swollen, tender, stiff and painful on forced motion. Fingers and left metatarsals were swollen and tender. The right knee was swollen, stiff, tender and painful. Other joints were less affected. Roentgenograms revealed changes only in soft tissues.

Physical therapy and analgesics were given, without relief.

Use of Control Material.—Cholesterol was given for six days (January 19 to 24). The arthritis increased. Sedimentation rates continued to increase. The patient slept fitfully and was wakened frequently by pain. He needed help getting off the toilet. On January 22 he could hardly get out of bed, even with help; once up he walked only two steps because of a painful right knee, and then he returned to bed. The next day his left knee swelled. He had lost 7½ pounds (3.4 Kg.) in three weeks.

Effect of Cortisone.—Cortisone acetate was given for sixty-one days (January 25 to March 26). The first day the patient received 300 mg.; then 100 mg.

daily for seven days; 200 mg. for thirty-five days; 100 mg. for seven days, and 50 mg. for 11 days (fig. 18).

On January 25, just before his first dose of cortisone, he was "miserable." That morning he had to have help to get the bedclothes off his feet, could not put on his bathrobe and made six attempts before rising alone from the toilet. Motion pictures were made that morning. He received his first injection (300 mg.) at 2 p. m. About four hours later he was much less stiff. At 9:30 p. m. he got out of bed easily and "stepped right out." He managed his toilet easily, and, the radio being on, he "tested out" his joints by dancing around the room for five minutes. That night he slept painlessly and in the morning rose without stiffness or pain. At 9 a. m. the morning after his first injection we asked him how he felt.

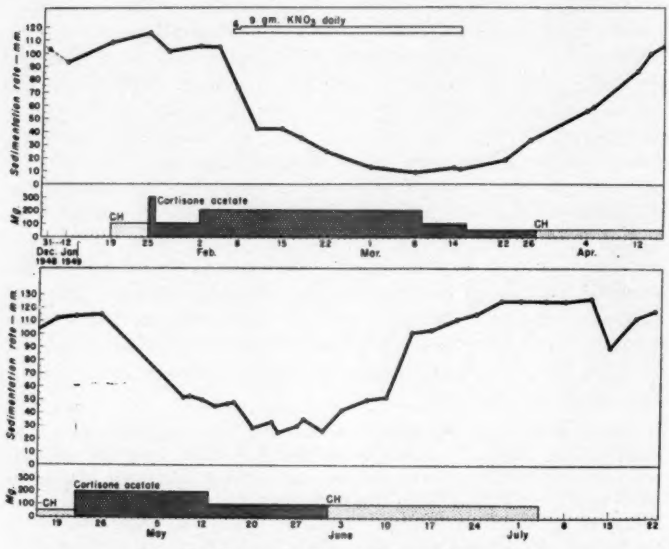

Fig. 18.—Curve of sedimentation rate in case 10.

At first he did not reply, but while lying in bed he arched his back in a half somersault and planted his feet over his head flat on the wall behind his bed. Then he said, "This is a new fellow. This morning I shaved normally and can put my arm behind by head." We reminded him that he had been receiving "injections" for seven days and asked him to be precise about the time of improvement. He replied: "It came on slowly yesterday afternoon, more rapidly last night. I have no idea why I didn't start getting better till yesterday."

His response was such that motion pictures were again made that afternoon. At the studio the day before he had to be helped to undress and was "hoisted" off the couch. This afternoon he dressed alone in fifteen minutes, undressed easily and got up at will.

After three days of use of cortisone he had lost the aching and most of his weakness, stiffness, articular pain and tenderness. Swelling of left knee and

metatarsals had almost disappeared; that of right knee, wrists and fingers was notably reduced. But during the next four days the shoulders and knees remained slightly painful on motion. Because of this and because his sedimentation rate had fallen only 10 mm. in eight days, despite the marked subjective improvement, he was given 200 mg. daily. After three days on the increased dosage his sedimentation rate fell, at first precipitously (62 mm. in six days) and then more slowly; it was normal on March 1.

With minor daily variations his improvement was maintained during the thirty-five days he was given 200 mg. daily (February 2 to March 8). The increased dosage appeared to augment the improvement (unlike case 14). The patient walked as much as 1 to 2 miles daily. The knees became practically painless, almost free of swelling and normally mobile (fig. 19).

After cortisone was first given, the patient took as much as 5,000 cc. of fluid daily; some nocturia occurred. There was no glycosuria, and results of glucose tolerance tests remained normal. Within a few days after the doses of cortisone were doubled moderate edema of the legs developed and the patient gained 5 pounds (2.3 Kg.). Potassium nitrate, 3 Gm. three times a day, was given and intake of fluid was restricted. Within a week he lost 6 pounds (2.7 Kg.) and the edema almost disappeared. A little fuzz appeared on his bald head. He thought that his beard was stiffer, and he shaved daily instead of every other day. Because of obesity his diet comprised 1,500 calories daily; thereafter he slowly lost weight.

After receiving cortisone for forty-three days he had an estimated 95 per cent loss of symptoms; the sedimentation rate had fallen from 115 to 9 mm. Residuals were slight (grade 1) stiffness of the right knee and lumbar portion of the spine. Otherwise all swelling, pain at rest, tenderness, stiffness and pain on forced motion had disappeared. During a recent visit of his wife the patient had noticed decreased libido and potentia, although intercourse was satisfactory. Daily doses of cortisone were reduced to 100 mg. for a week (March 9 to 15) and then to 50 mg. for eleven days (March 16 to 26). The sedimentation rate remained normal for a few days after the doses of cortisone had been reduced to 50 mg.; then it increased rapidly.

Use of Control Material.—Cholesterol was given again for twenty-six days (March 27 to April 21). Symptoms did not increase until March 30: between then and April 20 the wrists and knees were slightly swollen and tender.

About March 30, after four days without cortisone, frequent frontal and maxillary headaches, occasional tinnitus and transient "fuzzy vision" developed. Despite this, the patient felt good generally and continued walking a mile or two daily. After he had gone sixteen days without cortisone, an acute febrile polyarticular flare-up developed and five days later left popliteal thrombophlebitis, for which dicumarol,* heparin and penicillin were given. This and febrile arthritis continued until the use of cortisone (200 mg. daily) was begun again on April 22.

Cortisone.—Second Course: Cortisone acetate was again given for forty days: 200 mg. daily for twenty-one days (April 22 to May 12); 100 mg. daily for nineteen days (May 13 to 31). The second response closely resembled the first in that most of his subjective and objective manifestations quickly disappeared. The sedimentation rate decreased from 114 to 52 mm. in seventeen days. It was 26 mm. on May 31. Articular relief was estimated at "90 to 95 per cent." There were practically no residuals. No significant edema developed during this course. Whereas the growth of hair and beard apparently increased slightly during the

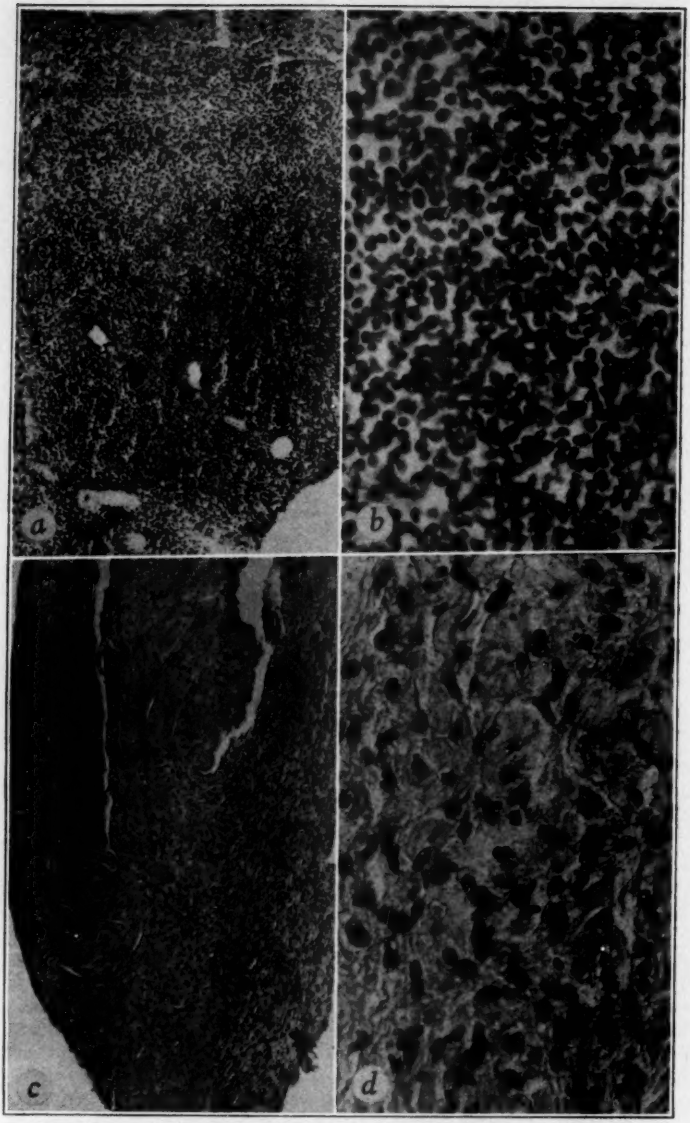

Fig. 19 (case 10).—Synovia of right knee before cortisone was given, to be compared with synovia from same knee taken after thirty-nine days of use of cortisone. (*a* and *b*) Before cortisone there was marked inflammatory reaction in the synovia, the focal collections of lymphocytes and the collection of fibrin on the surface of synovial membrane. Hematoxylin and eosin; × 70 and × 400. (*c* and *d*) After thirty-nine days of use of cortisone, the synovia is not yet normal but the fibrin layer on the synovia has disappeared and the cellular reaction has changed to fibrous healing. Hematoxylin and eosin; × 70 and × 400.

first course of cortisone and decreased when use of cortisone was discontinued, no stimulation of growth was apparent during the second course.

Each year for many years the patient had had moderately severe hay fever beginning late in April and lasting until frost, but worse in May, June and July. He could not sleep at night near an open window. But in the hospital he slept with his bed beside an open window and had no hay fever at any time.

Second Use of Control Material.—The patient remained in the hospital fifty-two more days, during the first thirty-three of which cholesterol was again given. Sedimentation rates increased rapidly. Rheumatic symptoms increased slowly, no more rapidly than after the first course.

Late in June and in July muscular weakness was disproportionate to arthritic symptoms. At the time of dismissal (July 23) the patient was walking as much as eighteen blocks daily. After 10 weeks without cortisone he still maintained an estimated 75 per cent of his over-all improvement, despite his very high sedimentation rate.

Follow-Up.—During August rheumatic symptoms varied. He was free of hay fever. He walked 1 or 2 miles daily. His sedimentation rates (Westergren) were reported as being 67, 58, 22, 35 and 26 mm. on August 24, September 16 and 30, October 14 and December 23, respectively.

Summary.—In this case each time cortisone was given the rheumatic symptoms responded promptly and sedimentation rates more slowly. Polydipsia and moderate dependent edema developed early in the first course; the edema practically disappeared when fluids were restricted and potassium nitrate was given by mouth. Seventeen days after the first course the patient had a short febrile flare-up of arthritis while receiving injections of cholesterol. This was followed by tenderness in the region of popliteal veins. A diagnosis of thrombophlebitis was entertained. Symptoms did not subside until cortisone was given again.

No edema developed during the second course. No acne occurred. Euphoria developed during each course. Cortisone appeared to control the patient's hay fever. Posthormonal fatigue lasting about a month developed about five weeks after the second course was completed.

GROUP 4: MARKED OR MODERATE ANTIRHEUMATIC EFFECTS WITH MARKED SIDE EFFECTS

CASE 14.—*Moderately severe rheumatoid arthritis; very marked results from ACTH; marked results from cortisone; side effects from cortisone in high doses; special studies with cortisone and estrone or testosterone*

Rheumatoid arthritis, after its onset in March 1944, soon affected practically all joints except the spine of this patient, a widow 45 years old. After roentgen therapy in December 1944, amenorrhea developed and persisted. In 1945 she was bedridden six months. In 1947 she gradually improved. In 1948 she was moderately disabled. Pain woke her often at night. Morning stiffness was "terrific to have to work off." She needed help to get into and out of a tub. Driving a car and buttoning clothes were difficult.

On admission to the Metabolism Unit of the hospital Jan. 21, 1949, many joints showed moderate or marked swelling tenderness and stiffness. She was "miserable."

Roentgenograms of metatarsal joints showed destructive changes. Sedimentation rates were 93, 100 and 93 mm. on February 2, 5 and 8.

Use of ACTH.—This was given, 100 mg. daily (25 mg. at 8 a. m. and 4 p. m. and 50 mg. at 10 p. m.), for twelve days (February 8 to 19) (fig. 20). Within about a week stiffness had disappeared, and tenderness and aching were decreased. After eleven days of use of ACTH the patient had complete subjective relief, an estimated over-all relief of 90 per cent. She had three consecutive days free of

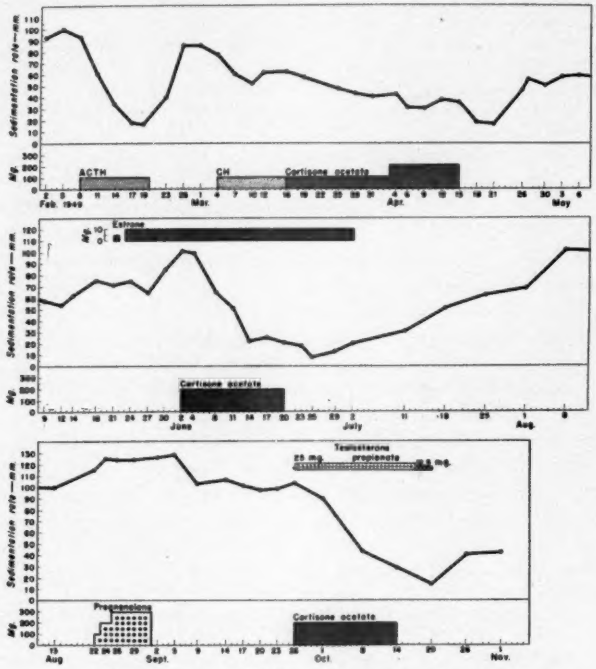

Fig. 20.—Curve of sedimentation rate in case 14.

pain, the first such in five years. The sedimentation rate fell precipitously 75 mm. during the first nine days on ACTH: from 93 to 18 mm. (February 8 to 17).

Although the antirheumatic effect was excellent, mild abdominal cramps, flatus, headache and sensation of fulness of the chest developed after each injection of ACTH. Also the patient was somewhat emotional and apprehensive. Within the first six days she gained about 5 pounds, but lost the same amount in five days.

Withdrawal of ACTH.—Three days after use of ACTH was discontinued articular symptoms returned and were as severe as ever for two or three days and then subsided; after twelve days without ACTH the patient regained perhaps three fourths of her improvement (March 4). The sedimentation rate increased

promptly. For a week after administration of ACTH was discontinued she complained of exhaustion, nervous tension, lassitude, palpitation and pain in chest.

Use of Control Material.—Cholesterol was given daily for twelve days (March 4 to 15). After the initial post-ACTH increase of sedimentation rate there was a secondary drop. Exhaustion disappeared, but mild pain in the chest continued.

Cortisone Acetate.—First Course: This was given for thirty days (March 16 to April 14): 100 mg. daily for eighteen days and 200 mg. daily for twelve days. On the third day improvement was noted. The next day (March 19) all pain at rest was gone and the joints were minimally swollen and tender.

After receiving 100 mg. of cortisone daily for about two weeks, the patient began to note restlessness, tension, fulness in the head, and transient blurring of vision so that momentarily she could not focus clearly. During the next four days the feeling of tension increased. She was unable to plan or concentrate. Most of her rheumatic pains had disappeared, but "deep aching as if in bones" developed. The sedimentation rate steadily decreased to 40 mm. on March 31.

On the 100 mg. doses she lost 95 per cent of her subjective, and most of the objective, rheumatic manifestations, an estimated over-all relief of 80 per cent. Doubling the dose did not appreciably increase this improvement. But it aggravated the unpleasant side effects. Bone pain increased. She had a curious combination of nervous energy and physical exhaustion. Feeling energetic, she got up early, made her bed, weighed herself, washed some clothes and read the morning paper, all before 7 a. m. Then she would write letters and perhaps read two or three magazines. By noon or later she was exhaused. She complained also of transient headaches, transient blurring of vision and soreness in the chest. About April 9, after twenty-four days of use of cortisone (six days of high doses), rounding of face was first noted. The sedimentation rate continued to fall slowly and became normal four days after use of cortisone was discontinued.

The foregoing symptoms constituted the most marked subjective symptoms of hypercortisonism which we have seen develop during a short term (thirty day) administration of the hormone and were associated with a marked hypopotassemic hypochloremic alkalosis. Blood electrolytes were altered thus: plasma potassium 2.8, chloride 96 and sodium 143 milliequivalents per liter; the carbon dioxide-combining power increased to 37 milliequivalents.

First Withdrawal of Cortisone.—Use of cortisone was discontinued after April 14, but it appeared as if the patient had accumulated incompletely absorbed deposits of cortisone at the sites of injection because the biochemical alterations just mentioned progressed for twelve more days, during which time the plasma potassium decreased to 2 and the carbon dioxide-combining power increased to 42 milliequivalents. Associated with the reduced plasma potassium was marked muscular weakness. In the electrocardiograms, voltage was decreased; the Q-T interval was increased to 0.28 second; T waves were isoelectric in lead I and inverted in leads II and III (fig. 21).

By May 3, nineteen days after cortisone was withdrawn, concentrations of plasma potassium and carbon dioxide were normal, as was the electrocardiogram. Weakness, transient blurring of vision and headache disappeared more slowly. During the seven weeks without medication the patient had mild rheumatic symptoms. The sedimentation rate increased.

Cortisone.—Second Course: Concomitant Use of Estrone. Because this patient had lost so much of her rheumatic disability during the use of ACTH and cortisone but had had notable symptomatic, physiologic and biochemical alterations therefrom and especially because artificial menopause had occurred after

roentgen therapy in December 1944, we were anxious to determine whether concomitant use of estrone or of testosterone would lessen or prevent the undesirable effects of cortisone while still not interfering with the antirheumatic effect.

Cortisone acetate, 200 mg. daily, was given for eighteen days (June 2 to 19). Estrone, 5 mg., was given on May 21; thereafter 10 mg. was given daily for thirty-nine days (May 23 to July 1). Thus estrone was given intramuscularly twelve days before, continued during and given twelve days after the use of cortisone.

Estrone alone had no antirheumatic effect. As soon as cortisone was administered, rheumatic symptoms began to disappear again. Within a few days the

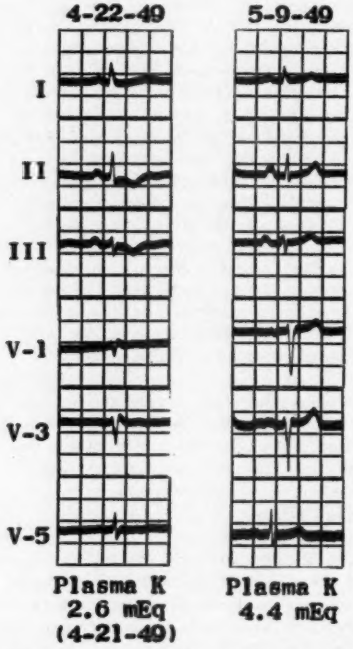

Fig. 21 (case 14).—Electrocardiograms. April 22, 1949: plasma potassium 2.6 milliequivalents per liter. There was a relation of hypopotassemia to the isoelectric or inverted T waves in all leads and depressed ST segment in standard leads II and III. May 9: plasma potassium 4.4 milliequivalents with rise in potassium to normal level since April 22. All T waves are distinctly upright. This is most striking in standard leads II and III and the three chest leads. There is also a rise in ST segments in normal leads I and II.

patient felt well. She took an automobile ride for two hours. She was hyperactive some days, irritable and tired on others. Articular swelling and tenderness again decreased markedly. The sedimentation rate dropped precipitously 79 mm. during the first twelve days of use of cortisone, continued to drop and was normal (7 mm.) on June 25. Although she tolerated these large doses of cortisone better with estrone than without and had few symptomatic side effects, hypo-

chloremic hypopotassemic alkalosis developed again and the systolic blood pressure rose 20 mm.

Second Withdrawal of Cortisone.—Use of cortisone was discontinued after June 19. Toward the end of June, while the patient was still receiving estrone, she was stronger and more active; "It's a pleasure to walk." There was no articular tenderness or swelling. The muscular weakness, "mental momentum," lightheadedness, burning sensations and transient blurring of vision slowly disappeared. On some days she spent many hours downtown shopping.

For about eleven days (August 4 to 14) she experienced the first menstrual bleeding in five years, presumably a delayed effect related to withdrawal of estrogen. By August 19 her joints had worsened somewhat but were better than on admission. The sedimentation rate had slowly risen again. By September 26, the patient needed help getting out of bed. Her appetite was poor.

Cortisone.—Third Course: Concomitant Use of Testosterone. Cortisone acetate, 200 mg. daily, was given for eighteen days (September 26 to October 13). Testosterone propionate was given daily during this time and for six days more: 25 mg. daily for twenty-one days and 12.5 mg. for three more days. Again the patient lost most (about 80 per cent) of the signs and symptoms of arthritis. The sedimentation rate fell precipitously, from 103 to 14 mm. in twenty-four days. Marked rounding of the face developed, more so than had occurred previously from cortisone or ACTH alone or from cortisone with estrone; the testosterone was considered responsible. The voice was unchanged. Slight growth of hair was noted on the upper lip. No striae or acne developed. The patient had an occasional restless day but appeared to have less weakness and other side effects than from cortisone alone or from cortisone with estrogen.

Withdrawal of Cortisone and Testosterone.—The sedimentation rate rose again. Eighteen days after use of cortisone was discontinued the relief obtained therefrom was still maintained. The patient was dismissed to her home on November 3.

Follow-Up.—She returned to office work seven weeks (December 3) after discontinuing use of cortisone. She only has mild rheumatic symptoms at present, four months after cortisone was discontinued.

Summary.—The antirheumatic effects of ACTH and cortisone were marked despite the undesirable reactions to these hormones. The patient lost practically all her subjective and most of her objective evidences of arthritis. Sedimentation rates became normal each time cortisone or ACTH was used.

Side effects from ACTH (100 mg. daily) were fairly mild. Disturbing symptomatic side effects and a marked hypopotassemic hypochloremic alkalosis developed from 100 mg. doses of cortisone and were aggravated by 200 mg. doses. Later some symptomatic side effects were less marked when estrone was given than were those during the use of cortisone (200 mg.), and still later they were largely minimized by the use of testosterone given during the use of cortisone (200 mg.). Detailed metabolic data on this case have been reported elsewhere.[22a]

Systolic blood pressure was not affected by 100 mg. doses of cortisone but was raised slightly (10 to 20 mm.) during the use of 100 mg. doses of ACTH and 200 mg. doses of cortisone. Diastolic pressure was not affected.

CASE 12.—*Moderately severe rheumatoid arthritis; effect of cortisone; very marked relief from arthritis but symptoms of hypercortisonism in first course; marked relief with second course; subjective side effects largely controlled by estrone*

A housewife, 43 years old, had backache with sciatica for three weeks in 1945. In May 1948 stiffness and pain developed in a shoulder and finger. Within two months many joints were affected. Thereafter the arthritis was chronic. Although married nineteen years, she was childless. Menses previously had been fairly regular except that she missed one or two periods yearly. She last menstruated December 18, 1948.

She was admitted to the hospital Feb. 3, 1949. Swelling and tenderness affected many joints. The right elbow was flexed 20 degrees. There was mild pretibial

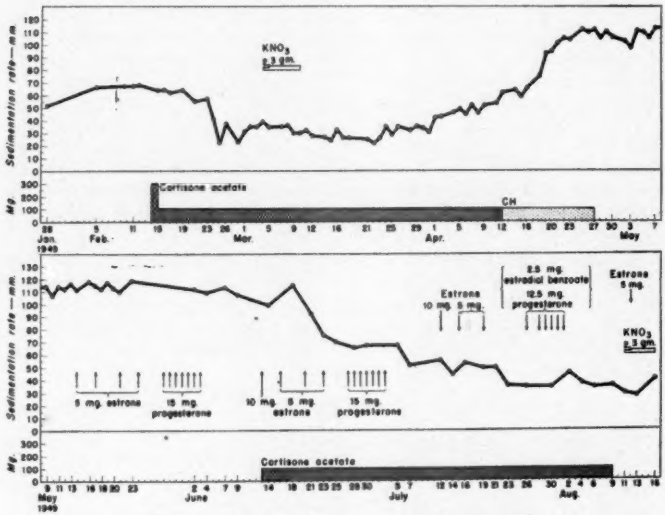

Fig. 22.—Curve of sedimentation rate in case 12.

edema. Roentgenograms of several joints revealed swelling of soft tissues and osteoporosis. Sedimentation rates were 52 mm. on January 28 and 66 mm. on February 5.

The patient became worse on withdrawal of acetylsalicylic acid. She could not write, knit, cut her food or dry herself after a bath. Sedimentation rates were 67 and 68 mm. on February 11 and 12.

Effect of Cortisone.—First Course: Cortisone acetate was given for fifty-seven days (February 14 to April 11): 300 mg. the first day and 100 mg. each morning thereafter (fig. 22). Within a week the patient was greatly improved. Most of the tenderness, all pain at rest and much of the swelling had disappeared. She got into and out of a tub easily and even cleaned it herself. Her appetite was "tremendous," and she gained 5 pounds in seven days. A sense of euphoria and increased energy were present.

The sedimentation rate, which was refractory during the first five days of cortisone, fell rapidly to 22 mm. on February 25. After two weeks of use of cortisone flexion deformity of the right elbow had disappeared. She spent four hours doing errands downtown. Relief from rheumatic symptoms was estimated as 95 per cent. But a week before this (about February 23, after ten days of cortisone), various annoying symptoms began to occur: first nocturia (urination two to five times nightly), then palpitation, pounding of the heart, heaviness of the chest, hot flashes, nervousness and dull morning bandlike headaches. On certain days she felt depressed. About March 2 her mild precortisone edema of the legs increased. About 7 a. m. she would have for about an hour a "spell" characterized by nervousness, bloating, apprehension and "heaviness" in the neck and chest, such that breathing and swallowing seemed difficult. Edema of the legs increased, and dependent edema was noted in sacral region. Potassium nitrate, usually 1 Gm. three times a day, was given for six days, during which time the

Fig. 23 (case 12).—Increase in fat at the cervicothoracic junction in this patient ("buffalo hump") after fifty-seven days of cortisone.

edema decreased somewhat. Output of urine exceeded intake of fluid by as much as 1,200 cc. per twenty-four hours, but she did not lose weight or obtain relief from distressing symptoms.

About March 10, she began to feel "jittery" and to have "butterflies in her stomach." Vision became slightly blurred. "Bone pain" was noted in the arms and legs and was not relieved by warm tub baths. She had no energy and tired on exertion. Her appetite was still "tremendous," but by restricting her intake of food to 1,500 calories and fluid she gained only 5 pounds during March.

To study these phenomena further, use of cortisone (100 mg. daily) was continued for eleven days in April. But by this time nocturia had diminished. The patient complained of thickening and tightness of the skin and subcutaneous tissues of the neck, upper part of the chest, shoulders and axillas, and thickening of retrocervical tissues was apparent ("buffalo hump," fig. 23). Fronto-occipital headaches occurred. The blood pressure remained normal. Rounding of the face and mild hirsutism appeared, and clothes became tight about the pelvis and abdomen.

The sedimentation rate had fallen to 22 and 23 mm. (February 25 and 28), risen slightly for a few days and then slowly returned to 22 mm. on March 22. But between March 22 and April 12, while the symptoms due to hormonal excess were becoming marked, the rate gradually rose again to 62 mm. on April 12, when use of cortisone was discontinued.

During March articular improvement had continued but was overshadowed by the symptoms just enumerated, particularly by the developing sensation of generalized stiffness of the skin and underlying soft tissues. Except for the right elbow, which was slightly flexed, joints were practically normal.

Use of Control Material.—Cholesterol was given daily for fifteen days (April 12 to 26). On April 13 morning stiffness returned. Three days later the patient had to use both hands to open a door and it was difficult to hold a newspaper in one hand. By the end of April two thirds of her articular tenderness and swelling had returned. The sedimentation rate rose fairly rapidly and was 112 mm. on April 25.

Most of the side effects began to disappear soon after use of cortisone was discontinued. The urinary output again exceeded the intake of fluid, and the weight remained constant. Rounding of the face became smaller, and visual blurring lessened. During May these various manifestations disappeared and the appearance of her face and neck was normal.

Special Studies with Estrone and Progesterone.—It was decided to make special studies on the effect of cortisone on gonadotropic function and menopausal symptoms. As stated before, the patient's last menses had been on Dec. 18, 1948. Estrone was given (5 mg.) twice weekly between May 13 and 23 and progesterone (15 mg.) daily between May 28 and June 3 (fig. 22). Endometrial biopsies were made at appropriate periods during the menstrual cycle. Abdominal cramps and a near normal menstrual flow occurred June 6 to 9. Although the patient felt stronger and was again walking about the hospital corridors, rheumatic symptoms and the sedimentation rate were not affected by estrone or progesterone.

Effect of Cortisone Given During Use of Estrone and Progesterone.—Cortisone acetate, 100 mg., was given daily for fifty-seven days (June 13 to Aug. 8). In addition, estrone was given twice weekly between June 13 and 22 and between July 12 and 19 (10 mg. the first dose and 5 mg. each dose thereafter); progesterone 15 mg. daily, was given June 27 to July 3. Estradiol benzoate, 2.5 mg., and progesterone, 12.5 mg., were given on six of the seven days from July 26 to August 1. These were given intramuscularly.

On the third day of use of cortisone, stiffness was much less and she wrote letters for the first time in several weeks. Within a week she was much better, and after another week she lost about 70 per cent of her symptoms. Swellings again disappeared from some joints and almost disappeared from the others. Tenderness was absent or minimal in all joints, but the wrists and metatarsals were still tender. The sedimentation rate fell rapidly at first and then more slowly to 67 mm. on June 30.

During July the patient's arthritis was markedly but never completely relieved: Some joints were symptomless; minimal thickening and tenderness were present here and there. Flexion deformity of the right elbow disappeared. Menstrual flow occurred July 5 to 9. She felt "very good," and her appetite was good. Sometimes she went downtown for shopping, dinner and the movies. She slept restfully without nocturia. She had no headaches, hot flashes, fulness and aching of the neck or chest, globus, dysphagia or weak spells. There was no hirsutism. Then for two weeks administration of estrone was discontinued; some of these

symptoms then returned for eight days. In mid-July slight edema of the lower extremities appeared and the face became slightly puffy. The edema increased and became marked, varying in intensity in relation to frequent diuresis and perhaps in relation to use of progesterone. She gained about 5 pounds in three weeks. Despite the edema she stated: "I feel very good; I sleep like a log and get right out of bed in the morning without stiffness. This time I have no spells of nervous energy or fatigue, no ups and downs. I feel normal. This is the combination for me."

The sedimentation rate continued to fall slowly to 34 mm. on July 31. During this course of cortisone occasional estimates of blood chlorides, carbon dioxide-combining power and sodium and potassium were normal. The blood pressure remained normal. On August 6 she shopped downtown, walking about 2 miles without symptoms except for minimal pain in the knees when she climbed steps or stepped up on street curbs. Menstrual flow began August 5 and lasted six days.

Second Withdrawal of Cortisone.—For two days after the last dose of cortisone the patient's condition was unchanged. During the next two or three days stiffness returned and she noted transient fulness or pressure in the neck and behind the eyes, with blurring of vision. The sedimentation rate soon rose. Potassium nitrate, usually 1 Gm. three times a day, for five days did not reduce the edema prior to her dismissal, on August 16. Moderate articular swellings and tenderness were present, but stiffness was minimal.

Follow-Up.—Later in August the arthritis increased, but in September there was improvement. In October she could shop at the neighborhood store, had no pain at rest or on moderate activity and morning stiffness lasted only ten minutes, but her legs felt weak, moderate edema of lower extremities persisted and when she was tardy in taking estrone she had occasional palpitation and hot flashes. She noted thinning of the hair and a "new crop coming in."

She was reexamined at the clinic on Dec. 13, 1949. She retained about a third of the improvement produced by cortisone. The sedimentation rate was 58.

Summary.—This patient received cortisone acetate during two courses of fifty-seven days each. Her rheumatic symptoms were almost completely abolished during the first course and markedly reduced during the second course. During the first course she tolerated the cortisone well for about two weeks. But thereafter a variety of symptoms developed, some of which were accentuated menopausal symptoms and others of which were probably manifestations of hypercortisonism. Prior to and during the second course of cortisone, estrone and progesterone were administered periodically. This did not prevent the recurrence of fluid retention and edema but seemed to prevent not only the menopausal symptoms but practically all the other undesirable effects that had occurred when cortisone was used alone. These effects included rounding of the face, mild hirsutism, general nervous tension, sense of substernal oppression and retro-orbital tension, difficult breathing, globus, headaches and periods of energy followed by exhaustion. The effect of estrone was further demonstrated by the partial return of some of these manifestations when the use of estrone was discontinued for

two weeks during the last half of the menstrual cycle. When estrone was readministered, these symptoms disappeared again. To date our studies on the effect of cortisone and ACTH on menstrual function by means of bioassay of urine for estrogens and gonadotropins, endometrial biopsy and vaginal smears have given disappointing results.

CASE 16.—*Very severe rheumatoid arthritis; cortisone given for one hundred and sixty-one days; moderate initial improvement; results unsatisfactory thereafter*

In May 1948 the shoulders of a man, 49 years old, had become painful and stiff. Several other joints quickly became affected. He soon was unable to work and a mild fever (temperature 99 to 101 F.) developed. He could walk only one block, could not get into or out of a tub and needed help in dressing and in cutting his food.

At the hospital on July 26, 1948 many joints were swollen slightly. Roentgenograms of several joints showed no significant abnormalities. Disability and debility were much greater than the objective evidence of arthritis, and sedimentation rates were 121, 103 and 116 on July 27 and August 2 and 9. Under treatment with physical therapy, analgesics and a high caloric diet, there was improvement, but sedimentation rates remained high. That winter the patient became worse, had to quit work again and became bedridden (January 15). He lost 25 to 30 pounds (11.3 to 13.6 Kg.) in a month.

Readmitted to the hospital on March 22, 1949, he was markedly disabled. He looked 10 to 15 years older than his 49 years. Except for "shuffling" to the bathroom he was bedridden most of the time and could turn in bed only with assistance. Generalized muscular atrophy was present. Swelling and tenderness of moderate degree affected most of the joints of the extremities, especially the fingers and the metatarsals. Roentgenograms, which just a few months before, on his previous admission, showed normal conditions, now revealed destructive arthritis of several joints. The sedimentation rate was 115 mm. (March 23). The weight was 126 pounds (57.2 Kg.), a loss of 40 pounds (18.1 Kg.) in six months. He derived little or no comfort from physical therapy, rest in bed and acetylsalicylic acid.

Use of Control Material.—Cholesterol was given daily for six days (March 28 to April 2). His painful condition necessitated use of at least ½ grain (0.032 Gm.) of codeine each night to supplement the acetylsalicylic acid. The sedimentation rate increased from 98 to 114 mm. (March 29 to April 2). Then use of acetylsalicylic acid and codeine was discontinued.

Use of Cortisone.—Cortisone acetate was given daily for one hundred and sixty-one days (April 3 to September 10): 300 mg. on the first day, 100 mg. daily for the next three weeks and varying doses thereafter. On the first morning he was brought to the conference room in a wheel chair and then lifted to a straight chair. It was impossible for him to rise. He was such a "dead weight" that it was difficult for one person to lift him to a standing position. He could take only one or two shuffling steps while being held up. The knees were flexed 15 degrees, the right elbow, 25 degrees and the left 35 degrees. On forced motion the right shoulder could be abducted only 60 degrees, the left 50 degrees and on voluntary motion only 30 each. Pitting edema of the feet was present.

Improvement began thirty hours after the initial injection of cortisone with decrease of pain and stiffness in the arms; the patient was able to raise his arms higher and at night slept uninterruptedly for six hours. On April 6 he rose from a chair alone for the first time in weeks. After five days' use of cortisone he felt

stronger and sat up on the side of the bed. Stiffness was markedly lessened and pain at rest had disappeared, but he was still "weak on his feet." Articular tenderness, though subsiding, was still fairly marked (grades 2 and 2+), and the sedimentation rate was still refractory (114 mm. on April 8).

During the second week's use of cortisone improvement continued. The sedimentation rate began to fall rapidly (to 48 mm. on April 18). On April 10 he shaved himself for the first time, but marked generalized weakness continued. At the photographic studio on April 15, he climbed the test steps without support; before receipt of cortisone this maneuver had not been attempted. But he could walk no more than 10 feet, and edema of the feet was still marked. The sedimentation rate was 41 mm. on April 21. After nineteen days of receiving cortisone (April 21), he reached his optimal improvement: Most of his stiffness and soreness and all his pain at rest had disappeared. Subjectively he considered his arthritis "about 80 per cent gone," with persisting weakness the main residual. Improvement in subjective feelings, in functional abilities and in sedimentation rate surpassed the objective improvement. We estimated his over-all improvement at about 50 or 60 per cent.

After nineteen days the patient's course was unsatisfactory. On the next day (April 22) there was a flare-up in his right knee for thirty-six hours. The sedimentation rate, which had been decreasing for about two weeks, began to rise rapidly. Two explanations for this relapse were considered: Either (1) the dosage was inadequate, or (2) the preparation of cortisone which he was receiving tended not to remain in suspension. The doses were increased: 200 mg. on April 25; 150 mg. daily for the next nine days (April 26 to May 4). Extension of the knees was increased 10 degrees; of the elbows, 25 degrees. The shoulders could be abducted about 20 to 30 degrees more than formerly, but the sedimentation rate continued to rise, and arthritis was moderately active. The doses of cortisone were again increased from 150 to 200 mg. daily for twenty-seven days (May 5 to 31). For the first ten days the patient seemed to improve. About May 9 some rounding of the face was noted. He got into and out of bed and walked to the bathroom, washed and shaved himself. He gained 17 pounds (7.7 Kg.) without increase of the precortisone edema of the feet, slept well and had lost much of his articular soreness. But the weakness, which had been present since his admission, continued. The sedimentation rate decreased from 105 to 71 mm. (May 5 to 17). Although he could still walk to the bathroom and shave himself, he often needed help getting into or out of a chair. Mild hypochloremic hypopotassemic alkalosis was noted between May 27 and June 10. Because of the continuing edema, potassium chloride was given (30 grains [1.94 Gm.] three times a day) for eight days (May 29 to June 5).

Daily doses of cortisone were reduced to 100 mg. on June 1; this dose was given daily for eighty-eight days, as a single morning dose for the first sixty-one days and 50 mg. twice a day for the next twenty-seven days, through August 27.

After doses of cortisone were reduced on June 1, the patient's arthritis gradually increased. The blood pressure varied widely, systolic from 110 to 160 mm. and diastolic from 60 to 90 mm. Testosterone propionate was given for eleven days (June 6 to 16): 50 mg. the first day and then 25 mg. daily for ten days. This was given to see whether it would decrease the weakness or enhance the effect of cortisone. No clinical improvement occurred, but the sedimentation rate changed as follows: 100 mm. on June 4; 110 mm. on June 6; 56 mm. on June 7; 61 mm. on June 8; 105 mm. on June 9, and 115 mm. on June 10.

To see whether salicylates would enhance the effect of cortisone, acetylsalicylic acid was given (15 grains four times a day) from June 21 to July 5 and July 15

to August 9. For two weeks the patient improved; he walked around his room with a cane; articular swellings and tenderness were reduced more than previously, but sedimentation rates remained between 110 and 120 mm. On June 29 and July 30 blood smears showed myeloid immaturity and leukemoid reaction. Sternal marrow on July 1 and August 1 were essentially normal.

During the rest of July the daily dose of cortisone was given about 9 o'clock each morning. He felt "let down" between 10 a. m. and 2 p. m. and much better each afternoon. During August cortisone was given: 50 mg. twice a day instead of 100 mg. once daily. But this made no definite difference. The rheumatic variations were of much less concern than the continuing weakness, the cause of which was uncertain. On August 12 sharp pain and tenderness developed in the left side of his neck and over the shoulder. There was transient dyspnea and tachycardia. The pain lasted two days.

Between August 28 and September 10 the daily doses of cortisone were reduced to 25 mg. twice a day. During this time the patient's joints remained about as before, but about September 4 he began to have attacks of paroxysmal tachycardia two or three times daily, each lasting thirty to sixty minutes.

Withdrawal of Cortisone.—The use of cortisone was discontinued after September 10. Tachycardia became persistent. Edema of the extremities (present before admission) increased; gallop rhythm and some dyspnea developed, and treatment for cardiac decompensation was given between September 13 and October 12. Results of a congo red test for amyloid disease were negative. Serum electrolytes were usually essentially normal. On October 9 the serum potassium fell to 2.6 milliequivalents per liter, and electrocardiographic alterations were compatible with this reduction of serum potassium. Examination of ocular fundi revealed mild arteriolar sclerosis of a chronic hypertensive type. By mid-October the patient's cardiovascular function was well compensated. Cardiologists concluded that the cardiac failure probably resulted from coronary sclerosis because of the patient's senility disproportionate to his age, the occurrence of cardiac decompensation in a resting patient and the appearance of a fairly definite tick-tock rhythm. More experience is needed before one can suggest whether or not the cardiac complications were related to cortisone.

After use of cortisone was discontinued, articular swelling and stiffness increased moderately. Episcleritis of the right eye developed about three weeks after cortisone was withdrawn and persisted. Sedimentation rates rose slightly and remained between 127 and 132 mm. The patient returned home November 15 to continue symptomatic treatment and chrysotherapy. About January 15 he had a "heart attack," from which he died January 31.

Summary and Comment.—This was our most debilitated and disabled patients. Besides premature senility, other unusual features present on admission included edema of the lower extremities, rapid sedimentation rate and especially the weakness and exhaustion which were always a major factor both before and during the use of cortisone. The initial antirheumatic effect of cortisone was fairly satisfactory; within nineteen days he lost most of his subjective rheumatic symptoms, the sedimentation rate fell rapidly and although some tenderness and swelling remained his over-all improvement was perhaps 50 to 60 per cent, an amount less than that of any other patient, all of whom were less severely affected. Thereafter the patient's course was unsatisfactory.

At times residual tenderness and swelling were minimal, but minor flare-ups here and there were frequent.

The patient's weakness always dominated the clinical picture. The cause of the weakness was not clear. It was severe before admission and continued to be severe during and after the use of cortisone. Variations in the patient's weakness could not be correlated with alterations in serum potassium, and the weakness was not lessened by the administration of potassium chloride or testosterone. After the patient had received cortisone for about twenty-two weeks, attacks of paroxysmal tachycardia developed. After cortisone was discontinued cardiac decompensation presumably related to coronary disease, occurred and lasted three or four weeks, then it disappeared. Rounding of the face was noted about May 9, was marked in October and receded in November after the use of cortisone was discontinued. The patient died from a heart attack two and a half months after dismissal.

CASE 1.—*Severe rheumatoid arthritis; marked effect of prolonged administration of cortisone, given daily for one hundred and eighty-seven days*

A 28 year old housewife reported that in May 1944 she had completed a full term pregnancy complicated by albuminuria, hypertension, edema and a gain of 66 pounds (29.9 Kg.). After delivery, these symptoms disappeared. In October 1944, arthritis began and was progressive after October 1945. Penicillin, neostigmine, tonsillectomy, gold salts, streptomycin and Bogomolets' antireticulocytotoxic serum were relatively ineffective. A second course of gold was given. By February 1947 she was slightly improved. In January 1948 the disease spread and the right hip became worse.

Menses often occurred one week late. The patient's joints were worse a few days before menses and better the last two days of her menses. When menses were scanty, as they usually were, premenstrual aggravation of the articular condition was worse than when flow was normal.

First Two Admissions.—On the patient's first admission to the clinic, Feb. 16, 1948, she was moderately obese, weighing 155 pounds (70.3 Kg.). Many joints were affected. The sedimentation rate was 55 mm. Roentgenograms revealed destructive arthritis of the right hip, some destruction of cartilages of wrist joints and slighter changes, including osteoporosis, at other joints. Symptomatic treatment gave only temporary improvement.

After streptococcic pharyngitis in April 1948, the joints became worse. The patient returned to the clinic May 20, more disabled than before.

During June and July her joints again became worse. It took her till noon to limber up. She could do little housework; she was unable to make beds, iron clothes or push the electric sweeper. Her painful right hip caused a constant limp. She felt feverish.

Third Admission.—The patient was readmitted to the clinic and hospital July 26, 1948. Her temperature was 100 F. She walked slowly, stiffly and with a limp. The elbows were flexed: the right 20 degrees and the left 15 degrees. Maximal abduction of the shoulders was (right) 80 degrees and (left) 60 degrees. Motion of the right hip was moderately limited and painful. The knees and

other joints were swollen. Discouraged with orthodox measures she asked about other possibilities and was told of investigative procedures whereby remissions were sometimes induced as a result of lactophenin jaundice.

The liver was not palpable. Although there was no history of jaundice or hepatitis, tests of liver function suggested hepatic dysfunction. Sulfobromophthalein sodium tests showed 16 per cent, later 10 per cent, retention. The prothrombin time (Quick) was slightly increased: twenty to twenty-two (normal seventeen to nineteen) seconds. Cholesterol was 143 mg. and cholesterol esters 93 mg. per hundred cubic centimeters, both slightly low. The serum globulin was 4.35 Gm. per hundred cubic centimeters, producing an increased serum protein level of 8.97 Gm. The urinary excretion of porphyrins was increased to 354 (upper normal 80 to 90) micrograms.

Because of these findings, the patient was told that production of jaundice by lactophenin probably carried an increased risk in her case, but she elected to accept the risk. Before deciding to proceed, we performed a needle biopsy of her liver, which showed "practically normal liver tissue."

Although 34 Gm. of lactophenin was given orally between August 6 and September 3 (1 Gm. daily for ten days, 1 Gm. twice a day on six days and 1 Gm. three times a day on four days) no jaundice or other significant biochemical changes resulted. Sedimentation rates increased from 75 to 109 mm. on August 24 and 108 mm. on September 3. A little fever was present almost daily (the temperature usually 99 to 100, occasionally 101 F.).

At this time a small supply of compound E became available, and we decided to try it on this patient.

Effect of Cortisone.—Injections of cortisone (not the acetate) were begun Sept. 21, 1948 and continued in varying doses, uninterruptedly for one hundred and eighty-seven days, through March 26, 1949. Initial doses of cortisone were 100 mg. daily (50 mg. twice a day). On the morning of September 21, before the first injection of cortisone, the patient could hardly get out of bed; once she tried to walk; it was too painful, and so she remained at rest. But on September 23, after two days of use of cortisone, she woke with much less muscular stiffness and soreness, rolled over in bed easily for the first time in weeks and noted increased strength and appetite. Although she felt much better subjectively and the fibrositic component seemed to be much decreased, articular tenderness was unchanged. On the next day (September 24) improvement continued and we found her exercising, raising her hands over her head, previously impossible. She visited several patients to demonstrate her changed condition. Painful stiffness was gone. "My muscles feel stronger, and my appetite is very good." After six days of use of cortisone she had lost almost all her stiffness; articular tenderness and pain on motion were markedly reduced. The next afternoon (September 28) she shopped for three hours downtown, feeling tired thereafter but not sore or stiff. She noted a sense of well-being: "I have never felt better in my life." Despite the striking clinical improvement, the sedimentation rate was unaffected and was 111 mm. on September 27.

After eight days of 100 mg. daily doses, the dose was halved on September 29 (25 mg. twice a day). Menses occurred without aggravation of the arthritis. The improvement was maintained during four days of 50 mg. doses. To find a low maintenance dose, 25 mg. was given once daily for ten days (October 3 to 12). But these small doses were inadequate; symptoms increased notably. The sedimentation rate, which had fallen to 86 mm. on October 8, quickly rose to 117 mm. on October 12. Hence the doses were increased to 50 mg. once daily for two

days. Symptoms lessened but were still troublesome, and so 100 mg. was again given daily, 50 mg. twice a day (October 15 to December 28). The patient's condition again improved notably; she lost most of her stiffness and pain at rest, continued her walks around the hospital and ate heartily. About October 15 (when doses were increased) the previous mild fever began to subside; after October 24, the maximal temperature was 99 F. and after November 7 the temperature became normal and remained so.

Sedimentation rates at this stage were still fluctuating: 92 mm. on October 16; 115 mm. on October 19; then the rates fell rather rapidly after the 100 mg. daily doses were restored: 92 mm. on October 26, and 47 mm. on November 3.

At this early stage of our investigation the acetate ester of cortisone was being sent by Merck & Co. Inc., to Dr. Kendall, who removed the acetate radical and prepared crystalline suspensions of cortisone for our clinical use. Certain difficulties were encountered. The size of the crystals was not yet standardized. Many of the clinical and biochemical fluctuations which occurred in this case between October 1948 and January 1949 were due to variations in these early preparations.

Coincident with the use of an autoclaved aqueous suspension of fairly large crystals, on October 21, a definite rheumatic flare-up with a temperature of 101 F. developed. Despite this, she took short walks daily. Menses (October 30) did not aggravate the articular condition further. The flare-up reached its peak on November 2. Headache, fatigue, dizziness, tinnitus, anorexia and a "toxic feeling" developed for two days. The sedimentation rate increased markedly from 47 mm. to 108 (November 3 to 10). When another preparation of cortisone was used, rheumatic symptoms again diminished. On November 11 most of the joints were normal; the only residues were slight (grade 1) painless thickening of elbows, slight tenderness and aching in the right hip and left ankle. Sedimentation rates fell steadily: 71 mm. on November 17, 46 mm. on November 25 and 40 mm. on December 1. Her menses on November 26 were associated with a mild two day premenstrual aggravation of the joint condition, as had commonly occurred prior to the use of cortisone.

During December the arthritis was in almost complete remission with loss of about 95 per cent of rheumatic symptoms and signs. The patient had many hours and occasional whole days essentially free of all symptoms, but on most days she would have minimal or mild stiffness or tenderness here or there. She expressed the opinion that the morning dose (50 mg.) "failed to take hold" as promptly as the afternoon dose. Her December menses did not aggravate the joint condition. The sedimentation rate decreased slowly from 40 to 27 mm. (December 1 to 29).

This was the patient's best month. We had the impression that from the rheumatic standpoint a continuation of the daily doses of 100 mg. would produce complete remission in time or that a slightly increased daily dose would do this quickly. But we were unable to do either because of (1) lack of sufficient cortisone to increase the dose and (2) the slow development of certain side effects.

Onset of Side Effects.—Aside from the short flare-ups, presumably related to unsatisfactory preparations or inadequate dosage of cortisone, the patient tolerated well the first six weeks of use of cortisone. On November 1 she noted transient dizziness and we noticed that her face was slightly more rounded. About November 4 thirst was marked. The urinary output was less than the fluid intake. Tinnitus was noted. Whereas between July and October the patient had slowly lost 14 pounds (6.4 Kg.), she now gained 2½ pounds (1.1 Kg.) in three days (November 4 to 7). Thirst and tinnitus quickly disappeared; spontaneous diuresis

occurred; there was a 1 or 2 pound weight loss, and the patient's face became smaller. Her sense of well-being continued. About November 8 on wakening, she noted a "burning sensation beneath her skin" which disappeared a few minutes after she got up; this lasted only a few days. On November 11 she showed the first evidence of increased energy: She said, "I feel ambitious and want to be doing something all the time." Concentrations of blood sodium, potassium and carbon dioxide were normal.

The patient had mild acne prior to hospitalization. About November 12 this was slightly aggravated. Slightly increased growth of hair on the cheeks and at the hair line was noted November 20. On November 23, just prior to the menses, tinnitus recurred without headache or dizziness. Spontaneous diuresis occurred again for two days (December 11 and 12) and the face appeared to become smaller. On these same days transient "burning of skin" about the shoulders and arms and "tingling of fingers" lasted four or five hours; the patient considered these paresthesias related to the diuresis. She now eliminated extra salt from her diet. Within two days she suddenly gained 5½ pounds (2.5 Kg.) (from 141½ to 147 pounds [64.2 to 66.7 Kg.]).

The earlier of these various manifestations were mild, largely subjective and transient. But in view of the later disturbances of fluid balance it was decided to see once more whether smaller doses of cortisone would control the arthritis yet be devoid of other effects. On December 29 and for four more days, the daily dose was reduced to 50 mg. But spontaneous diuresis had already begun: The weight on December 29 was 5½ pounds (2.5 Kg.) less than that of the day before and within five days she lost 8 pounds (3.6 Kg.). The face and pelvis, which had become puffy, quickly receded in size. But with these smaller doses rheumatic symptoms increased. To determine whether 175 mg. instead of 200 mg. every forty-eight hours would be sufficient, the doses were varied after January 2 as follows: 75 mg. daily for two days, 100 mg. for one day, 75 mg. the next day, 100 mg. the next day, 75 mg. for four days, 100 mg. the next day (January 12) and thereafter 75 mg. daily for sixteen days, through January 28.

During January evanescent side effects continued. Some days the patient would feel energetic all day; on other days she would become very tired for two or three hours. Every now and then she would feel "jittery" or have transient tinnitus with or without dizziness or "mental fuzziness." Her appetite was excellent some days, only fair on other days. "Burning of the skin of the arms" accompanied the diuresis. Such paresthesias were abolished by motion. One day she noted that focusing her eyes for reading required voluntary effort. Probably because the average daily dose during January was about 75 rather than 100 mg., the face became slowly smaller, acne improved and the slight hirsutism did not increase.

There were too many variables during this manipulation of dosage for us to draw, in retrospect, any definite conclusions as to the exact relationship of the varying dosages and dose schemes to these symptoms. But the patient complained of fewer of them in the latter part of January, when she was receiving one daily dose of 75 mg., than in the earlier part, when the doses varied between 75 and 100 mg. or when the 75 mg. daily doses were being given in two or three divided doses. Through this period the sedimentation rate gradually rose (26 mm. on December 29, 64 mm. on January 19 and 53 mm. on January 26). The weight remained stationary at 139 ± 1 pounds. But rheumatic symptoms increased mildly in several joints and moderately in the right hip. Menses did not occur in January.

Cortisone Acetate.—Replacing cortisone, cortisone acetate was given as follows: 150 mg. on January 29; 100 mg. daily the next two days; 300 mg. on February 1, and 100 mg. daily thereafter through March 26. Sedimentation rates decreased

again: 66 mm. on February 2 and 36 mm. on February 16. Joints again became almost asymptomatic, although she usually had a little trouble somewhere. Her relief was estimated at about 90 per cent as compared with the 95 per cent improvement in December. "For the first time in at least a year" she could put her right foot on her left knee without discomfort to her right hip.

Although the joints were markedly improved and the sedimentation rates decreasing, the side effects continued and then increased. Diuresis seemed to follow a four day pattern. The patient would wake to note a burning sensation of the extremities and painless numbness and tingling of the hands which she described as being not in skin or muscles but "just beneath the skin." These paresthesias would last about four hours, during which diuresis occurred. For the rest of that day and for two or three more days she would feel much better. Occasionally she noted "jitteriness" or "shakiness," but there was no blurred vision.

Potassium nitrate was given, 6 gm. daily, for twenty-two days (February 8 to March 1), but this did not facilitate diuresis. Vitamin C, 600 mg. daily, was given for twenty-five days (February 19 to March 15).

On or about February 22 (after five months of use of cortisone) side effects became more marked, disturbing and significant. Her "nervousness," previously transient, became persistent and manifested by irritability and weepiness. Whereas her "low moods" had previously lasted only a couple of hours or so, she now became more persistently depressed and "unable to concentrate." Sedimentation rates, which had previously responded to her optimal antirheumatic doses of cortisone and had paralleled the rheumatic activity, now became "dissociated" and began to increase despite the continuing articular relief: the rate was 35 mm. on February 23, 60 mm. on March 1, 65 mm. on March 20, 41 mm. on March 24 and 64 mm. on March 26.

Some of the symptoms between February 22 and March 26 were an exaggeration of those which she had previously experienced; others were new and closely resembled those later seen in cases 12 and 14. From time to time the patient noted the following: bandlike pains around the thighs; transient "burning sensations" around a joint or in the buttocks; "pulling sensations" involving the nose, cheeks, teeth or skull; flashes of pain here and there; irregular pulse; generalized bone pain and tenderness; generalized "nonrheumatic stiffness"; heaviness of the chest; blurred vision (vision and fundi were normal). In the mornings she would be energetic but depressed; in the afternoon or evenings she would be exhausted but less depressed and at times even euphoric. But depression was more dominant than euphoria, and she began to worry about the future of her hip joint. The acne increased but was still mild. There was no pretibial edema, but generalized puffiness of tissues was present.

Special Studies.—Because of these unique developments, the patient was studied in the Metabolism Unit, but we found no biochemical explanation for her side effects. Her serum potassium was slightly reduced (3.5 to 3.8 milliequivalents per liter) occasionally in October and in early December, when cortisone was being given, but also in April, after use of cortisone was discontinued. The serum sodium and the carbon dioxide-combining power of the plasma remained essentially normal. The weight remained constant at 137 ± 1 pounds (62.1 ± 0.45 Kg.) between February and April. There was no significant increase in blood pressure at any time. No red striae developed; she had old white striae from the previous pregnancy.

Use of Control Material.—Cortisone was replaced on March 27 by cholesterol, which was given for sixteen days through April 11. Rather quickly the patient's mood changed. Three days after use of cortisone was discontinued, she was much

less depressed and stated: "My fear complex has changed to a hate complex. My reactions are more normal, and now I am angry at the thought of crutches and disgusted with myself for being upset." In walking she used crutches to prevent trauma to her hip, which she feared would become crippled. She went automobile riding each afternoon with her husband. Mental and physical relaxation began to replace the nervous tension. Fulness of the face began to recede in a week. (Since the picture of this patient was presented by Sprague and associates in the February issue of this journal, it has been omitted herein.) The bone tenderness had decreased markedly but articular swelling and stiffness became more prominent.

The sedimentation rate rose rapidly and was higher than on admission. It was 73 mm. on March 30, 60 mm. on April 2, 116 mm. on April 11 and 138 mm. on April 27. Then it fell to 94 mm. on May 4 and rose to 118 mm. on May 10, before she was dismissed.

The rheumatic symptoms returned in their distinctive way: first, fibrositic symptoms; later, articular pain and swelling. It became difficult for her to turn in bed, comb her hair or lift a glass. Acetylsalicylic acid and physical therapy were administered. Fever returned as before. The amenorrhea persisted. The patient began to "give up" and did not try to help herself as she had the previous fall. Then she rallied and became interested in the treatment she could have at home after dismissal. She went home May 10, 1949 to use physical therapy, analgesics and gold salts.

Mild weakness had been noted since the end of January; after cortisone was withdrawn this became more noticeable and may have been a withdrawal effect.

Follow-Up.—The patient did not respond to gold given for three or four months and was again bedridden. In the fall of 1949 she gradually improved. Menses occurred in August and September but not in October or November. Early in the summer her hair thinned out but later grew normally. The acne and hirsutism were about gone by December. She was afebrile, "in good spirits" and making some effort to become active. The sedimentation rate was 42 mm. in December.

Summary.—This patient, the first on whom the antirheumatic effect of cortisone was demonstrated, received cortisone continuously for a longer period (one hundred and eighty-seven days) than any other that we or others have studied so far. The initial effects of cortisone on her severe arthritis was marked. Almost bedridden just before the hormone was given, within a few days she lost most of her disability and also her fever. When we then attempted to find an effective smaller dose she had a quick relapse but responded again to the original dosage. Her satisfactory progress was interrupted by difficulties encountered in the preparation of our earliest suspensions of cortisone. Once these were overcome, she obtained an estimated 95 per cent relief of symptoms in December, after three months of doses of cortisone.

After she had received cortisone about six weeks, certain side effects began to develop: rounding of the face, mild aggravation of acne and mild hirsutism. During the next several weeks sudden shifts in water balance, a few transient paresthesias and amenorrhea developed. When the dosage was again lowered to avoid these effects, rheumatic symptoms increased. After certain adjustments of dosage an almost complete remission developed with an estimated 90 per cent relief of rheumatic

symptoms. But after five months of administration of cortisone, a greater variety of paresthesias and changes of mood developed, with depression dominating. A "dissociation" in the sedimentation rate began to occur, with rates increasing even though rheumatic symptoms were still largely controlled.

No biochemical explanation of these manifestations was uncovered. For some time before cortisone was given, the patient's menses had been somewhat irregular and she had had a toxemia of pregnancy. Whether some previously existing underlying hormonal disturbance played any role in her slow development of intolerance to cortisone is conjectural.

The side effects were reversible and disappeared, some quickly and some gradually, after use of cortisone was discontinued.

The initial development of euphoria from certain doses of cortisone and the contrasting eventual development of depression from further dosage appears to be worthy of intensive cooperative study.

GENERAL SUMMARY OF CASE MATERIAL

General Effect of Cortisone and ACTH.—As for the general effect (the antirheumatic effect in relation to the development or lack of development of side effects), results were thus: marked or very marked antirheumatic effects with no or minimal side effects, 9 cases; marked or very marked antirheumatic effects with mild side effects, 8 cases; marked or very marked antirheumatic effects with moderate side effects, 2 cases; very marked, marked or moderate antirheumatic effects with marked side effects, 4 cases.

Antirheumatic Effect.—Of the 23 patients who received cortisone or ACTH or both, 14 had very marked antirheumatic effect, 8 marked and 1 moderate.

Patients who received a very marked antirheumatic effect became more or less symptom free; they had practically no subjective symptoms, but minimal or slight objective evidence of arthritic activity was often present. To use a mathematical grading, they were relieved of about 90 to 95 per cent of their disability. Patients in whom the antirheumatic effect was marked were relieved of roughly 75 to 90 per cent of subjective and objective manifestations. They were often subjectively well but they also had days when they had mild arthritis.

Effect of Supplemental Measures.—As stated, supplemental measures were employed in a few cases, generally for about three weeks, in an attempt to augment the effect of cortisone. Vitamin C was given orally, 600 mg. daily, in 3 cases; acetylsalicylic acid was given in 2 cases. An infected sinus was eventually treated in case 2. In an attempt to modify menopausal symptoms and certain side effects, estrone, progesterone or

testosterone was given in 3 cases (cases 12, 14 and 16) during courses of cortisone. None of these measures appeared to augment the antirheumatic effect of cortisone or to affect sedimentation rates. The rationale for use of vitamin C was based on the possibility that it might retard the rate of catabolism of cortisone.

ANTIRHEUMATIC EFFECTS OF CORTISONE

Among the 21 rheumatoid patients who received cortisone or cortisone acetate, 12 had very marked, 8 had marked and 1 had moderate antirheumatic effects, irrespective of individual courses.

A total of thirty-five courses of cortisone, varying from eight to one hundred and eighty-seven days in duration, were given to these 21 patients, antirheumatic responses having been very marked in fifteen courses, marked in eighteen courses, moderate in one and mild (doses only 25 to 50 mg.) in one.

The Immediate Response to Cortisone.—In all cases the immediate pattern of improvement was characteristic. Within a few days there were marked reduction of muscular and articular stiffness, lessening of articular tenderness, aching and pain on motion and usually reduction in articular swelling. In general, within the first week stiffness, aching and pain on motion were markedly or completely relieved; within the second week articular tenderness and swellings were reduced or disappeared. Sometimes articular swelling began to recede early, within the first three or four days and disappeared completely within a week or two. In other cases reduction of swelling was tardier and less complete.

Maximal Responses.—Improvement developed in three stages. The striking initial subjective improvement generally developed within the first eight days; the maximal initial objective improvement usually developed within the first two to three weeks. Thereafter, use of cortisone being continued, further improvement appeared gradually but was sometimes interrupted by minor flare-ups, "arthritis in miniature." The maximal over-all improvement sometimes developed after two or three months of cortisone.

Relation of Dosage to Initial Effect and Maximal Effect.—The first day's dose in early cases was 100 mg. of cortisone (not acetate); in later cases, usually 300 mg. of cortisone acetate. Regardless of the severity of arthritis, the onset of improvement was unusually prompt (in three to fourteen hours) in most of the cases in which the initial dose was 300 mg. and usually a day or two later in those in which the initial dose was 100 mg. of cortisone or cortisone acetate. A 300 mg. dose on the first day did not hasten significantly the maximal response.

Repetition of the Pattern of Improvement.—When patients had two or more short or long courses of cortisone, the pattern of initial improvement was essentially the same in each course: first, reduction of stiffness and pain on motion; then, of aching, and then, of tenderness and swelling.

Effect on Flexion Deformities.—Fifteen of the 21 patients given cortisone had flexion contractures of one or more joints, some of which were marked. Of 31 contractures to which we paid special attention, 21 (68 per cent) disappeared completely, sometimes within three to seven days, sometimes within two to three weeks. The remaining 10 were all markedly decreased but not completely corrected. Some of these deformities were of relatively short duration, a few weeks or months, but others had been present for two to five years. In a few cases deformities disappeared during the use of cortisone and recurred thereafter. Thus, in case 6, flexion deformities of the knees practically disappeared quickly during use of cortisone, reappeared, disappeared during use of ACTH, reappeared and then almost disappeared again when compound F was given. In most cases they recurred only partially or not at all during the time patients were under observation and to date.

The improvement in 29 of these 31 flexion deformities was due solely to cortisone, but in a very severe case (case 23) sand bags and physical therapy were employed in an attempt to straighten residual flexion deformities in the knees. The slowest response was in the shoulder in case 2: Abduction before cortisone was given was limited to 15 degrees; after use of cortisone, to 90 to 100 degrees.

Effect on Rheumatoid Nodules and Lymph Nodes.—Several rheumatoid nodules and enlarged lymph nodes diminished in size during the use of cortisone; a few small ones seemed to disappear.

ANTIPYRETIC EFFECT OF CORTISONE

Fever usually disappeared when cortisone was given. In case 6 fever disappeared each time either cortisone or ACTH was used and reappeared after each course.

NUTRITIONAL EFFECTS OF CORTISONE

Characteristic of rheumatoid arthritis is loss of appetite and weight. One of the earliest effects of cortisone was stimulation of appetite with gains in weight.

Appetite.—Of the 21 rheumatoid patients given cortisone, 20 had increased appetites. The increase was very marked in 11 patients, whose appetite became "tremendous or insatiable." They often ate double meals or between meals. The diet of 1 such patient was checked: When

allowed to eat at will, he consumed about 6,000 calories a day. Increase in appetite was marked in 5 patients who were "very hungry." It was moderate in 4 other patients, whose appetite was "good but not ravenous."

The effect of cortisone on appetite bore no obvious relation to the effect on joints. Some patients whose joints were markedly relieved noted moderate change in appetite. Appetite was sometimes increased more during one course than during another without apparent relation to the plan of dosage.

Gains in Weight.—Patients receiving cortisone experienced two types of gain. Nutritional gains in weight were steady and progressive, not fluctuant, were proportionate to the increased appetite and did not diminish quickly when use of cortisone was discontinued. In contrast, gains in weight from retention of fluids were often associated with polydipsia or some visible edema of the lower extremities and were sometimes unaccompanied with increased appetite. Gains in weight due to "invisible edema" sometimes disappeared quickly within a very few days after the doses of cortisone were reduced or discontinued. Some patients showed both types of weight gain. It was not always easy to distinguish between the two types or to estimate (at least until use of cortisone was discontinued) how much of the increased weight was nutritional or otherwise.

Fairly marked nutritional weight gains were made by several patients; some who received cortisone for long periods gained weight progressively, and several accepted low calory diets to avoid obesity. The distribution of the added weight was general or abdominal. Two male patients who received cortisone for two hundred and fifteen and two hundred and eighteen days respectively acquired "paunches": 1 gained 41 pounds (case 2); the other 16½ pounds during his first nine weeks of use of cortisone and then went on a diet to prevent further gains (case 3). In several patients who gained weight steadily full faces of normal configuration developed, not the rounded face of Cushing's syndrome.

Other gains in weight, given in relation to the duration of cortisone administration, were: 8 pounds during twenty-nine days of cortisone (case 13); 14 pounds during twenty-two days (case 20); 18 pounds during sixty-six days (case 19); 19 pounds during thirty-two days (case 22); 26 pounds during one hundred and thirty-three days (case 5), and 32 pounds during sixty-four days (case 15).

EUPHOROGENIC EFFECT OF CORTISONE

A marked sense of well-being was experienced by 14 of the 21 patients given cortisone. Euphoria developed during each of two courses in 3 cases. It has been suggested that this sense of well-being was not

a true euphoria but simply a psychologic lift related to the sudden relief. A special study is being made by our colleagues Drs. F. J. Braceland and H. P. Rome, of the Section on Psychiatry. Their preliminary studies have suggested that the degree of euphoria is directly related to the amount and rapidity of the articular relief obtained and that the euphorogenic effect of cortisone is an indirect one.

It is our impression that this euphoria represents not mere relief from pain but is a positive factor accompanied with increased mental capacity and activity. One patient, a physician, while receiving cortisone quickly finished writing two medical papers which he was previously too distracted mentally to finish. One patient, a chemist, wrote a chemical paper while in the hospital. Another patient read "heavy literature" while receiving cortisone; after use of cortisone was discontinued he could not concentrate, even on detective stories.

The increased mental activity and energy were translated during the day into increased physical activity, sometimes during the night into what patients described as "thinking spells" which produced "comfortable insomnia," despite which they were not tired in the morning. As part of the euphoria, some patients had a feeling of restrained happiness without nervousness. One patient during each of two courses manifested an attitude of almost unrestrained gaiety and near exaltation.

DEVELOPMENT OF SIDE EFFECTS DURING THE USE OF CORTISONE

Side effects produced by cortisone will be discussed later in conjunction with those related to the use of ACTH.

THE CLINICAL PATTERN OF WITHDRAWAL OF CORTISONE

General Pattern.—When cortisone was withdrawn, rheumatic activity returned, in most cases rather quickly. The pattern of these relapses was, with a few important exceptions, characteristic. Generally within one to four days muscular and articular stiffness reappeared, the patient's appetite diminished, his energy was replaced by fatigue and sedimentation rates increased. Shortly thereafter articular aching, tenderness and painful motion recurred; then after a week or two swellings increased.

There were important exceptions to the general pattern of quick relapse. In some of our patients the relapse was delayed significantly, and in a few patients partial or even rather complete remissions continued for some weeks or months after cortisone was withdrawn. The clinical responses following withdrawal of cortisone (considering the end result after the last course in those who had more than one) can be grouped as follows: "Prompt rebound relapses," in that marked painful stiffness returned quickly and sedimentation rates rose promptly, developed in 2 patients who superficially appeared to be worse than they

had been before the hormone was given. But analysis of these 2 cases (cases 8 and 9) showed that, although some features were as bad as or worse than before, others were not so bad.

Fairly prompt relapses developed in 9 of the 21 patients given cortisone. In these cases relapses were fairly complete within a week or two (cases 1, 3, 4, 15, 16, 19, 20, 21 and 23). Delayed relapses developed in 5 patients (cases 6, 10, 12, 14 and 22); these patients retained most of their relief for from two weeks to a month or so. "Temporary remissions" resulted in 3 cases (cases 2, 11 and 13). In these cases most of the relief was retained for several weeks to several months. A "prolonged remission" resulted in 2 cases (cases 5 and 7).

Rebound Relapses.—The rebound relapse has been tentatively explained as follows: On injection cortisone depresses adrenal cortex function; hence when injections are suddenly stopped, the adrenal cortices may be temporarily secreting less cortisone than before the injections and continue to do so until the cortical function is restored, which apparently begins to occur usually within a few days. If this temporary deficiency is great enough, a rebound relapse occurs, which lessens as soon as cortical function is reestablished. In most of our cases this presumed temporary adrenal cortex insufficiency was not great enough to produce a severe articular flare-up, although it was often great enough to permit sedimentation rates to become more rapid than before the injections (a "humoral flare").

Sometimes the immediate relapse was soon followed by a secondary remission, which, though usually incomplete, was fairly marked. In some such secondary remissions only symptoms diminished; in others sedimentation rates also decreased.

Delayed Relapses and Remissions.—A delay in the return of symptoms could occur in different ways, for example, (1) from a continued utilization of incompletely absorbed cortisone in intramuscular deposits or (2) as a result of an authentic improvement in the status of the patient. In 2 cases symptoms returned more slowly and less completely after the second course than after the first course of cortisone. In case 12 the patient received 5.9 Gm. within fifty-seven days during the first course and 5.7 Gm. within fifty-seven days during the second course. Thus the courses were essentially equal in dose and length. After the first course most of her disability returned within nineteen days. After the second course much of her disability returned within two or three weeks but then she improved considerably for several weeks.

Case 11 was of special interest. The patient was first given cortisone, 1 Gm. in eight days, after which the sedimentation rate rose quickly and much of her disability returned within a week. She was

23. Deleted by author.

then given ACTH, 105 mg. daily for twelve days, after which the sedimentation rate again rose quickly; after a short articular flare-up, she regained most of the relief for two or three weeks. Later she was given a second course of cortisone, 200 mg. daily for eighteen days. After this course the sedimentation rate remained normal for about a week and the patient remained symptom free for three weeks and almost symptom free for about six months more.

One may argue that the more prolonged effect from the second course of cortisone in case 11 resulted from its greater length and dosage. But the evidence at hand does not suggest that doses of 200 mg. build up tissue depots which will supply cortisone for more than a few days. Hence it does not seem likely that the prolonged relief in case 11 resulted from tissue depots. It seems more likely that in this case and in case 5 something approaching a true remission was induced.

Even more striking was the result in case 7, that of a badly disabled woman who received one course of cortisone, 100 mg. daily for twenty-five days. She recovered almost completely and, despite a rising sedimentation rate, has retained practically all her symptomatic relief to date, a year after cortisone was withdrawn.

EFFECT OF CORTISONE ON SEDIMENTATION RATE

In every case sedimentation rates were reduced when cortisone was given. Rates became normal in 15 and almost normal in 3 of 21 cases. In the 3 remaining cases rates were reduced but did not become normal within the time of cortisone administration.

Relation Between Dosage and Effect on Rates.—There was a general but not an absolute relationship between dosage and effect on rates. Usually in these severe cases daily doses of 25 mg. were ineffective and of 50 mg. were ineffective or only partially effective; continued daily doses of 75 mg. had limited effectiveness. Rates were usually notably affected by doses of 100 mg. or more daily. Higher doses, of 150 or 200 mg., given for a few days appeared to increase the rate of fall in some cases (cases 10 and 14) but in other cases did not appear to be superior to 100 mg. doses (cases 11 and 13). Rates were often transiently refractory and did not begin to fall until after three to eight days of use of cortisone. Although an initial large dose of 300 mg. on the first day usually hastened the onset of symptomatic improvement, it did not accelerate the reduction of rates, reduce their tendency to be refractory for the first few days or shorten the refractory period. Thus while the superiority of 100 mg. daily over smaller doses seems established, so far as reduction of rates is concerned, the superiority of doses larger than 100 mg. daily is not definitely established.

Refractory Rates.—Doses that controlled adequately the rheumatic symptoms usually reduced rates satisfactorily but not always. An

associated type of refractoriness was present when both sedimentation rates and rheumatic symptoms were refractory or unresponsive to ineffective or inadequate doses of cortisone. A dissociated type of refractoriness was present when the doses were sufficient to affect symptoms but not rates. Transient initial refractoriness of the dissociated type was common. It occurred in about 60 per cent of instances when a course of cortisone was begun. Even though symptoms were responding satisfactorily to 100 mg. doses, rates were refractory (remaining elevated or even increasing) for a few days (usually three to eight days, average four to five days). Then they began to fall, usually without an increased dosage. Persistent dissociated refractoriness rarely occurred when daily doses of 100 mg. or more were used and was observed in only 3 cases (cases 2, 16 and 19).

That rates should respond to cortisone more slowly than the fibrositic or even the synovial component of rheumatoid arthritis is not surprising when one considers the pathogenesis of the disease; fibrositic symptoms commonly antedate the appearance of synovitis, and the latter may be present for weeks or months before sedimentation rates become elevated. Contrariwise, many older remedies have influenced symptoms fairly soon or often and sedimentation rates more slowly or not at all. The altered mechanism responsible for abnormal rates is an advanced and, once present, less reversible component of rheumatoid arthritis than the fibroarticular features. Hence it is sometimes easier for cortisone to control the patient's symptoms than his chart.

Types of Response.—Because of many variables (different doses and schemes of dosage, different preparations of cortisone and cortisone acetate, including early nonstandardized preparations, and variability in the length of administration and in the time intervals between courses), no standard type of response of the sedimentation rate was obtained. Rates usually fell fairly promptly and rapidly, but the rate of decrease varied from patient to patient and from time to time in the same patient. When the courses were relatively short, there were roughly three patterns of response: (1) rapid or fairly rapid reduction of rates to normal (this was the usual pattern); (2) initial transient refractoriness and then a fairly rapid fall to normal or to near normal rates; (3) initial transient refractoriness and then a slow fall to normal or near normal rate.

When the courses were relatively long, there were four different types of response: 1. Rates quickly became normal and remained essentially normal as long as cortisone was given. Such ideal responses occurred five times in 2 patients and were associated with excellent clinical responses. In case 3 (first course) after October 18 sedimentation rates fell within twenty-two days to 3 mm. and remained normal

for forty-two days; during the second course, after January 10 the rate again became normal quickly and remained so for sixty-three days; during the third course, after May 6 rates became normal in twenty-five days and remained so for forty-nine days. In case 5, after December 24 the rate decreased to 11 mm. after twelve days and remained between 4 and 26 mm. for the next twenty-seven days. Later, after some reduction of dosage, during which the sedimentation rate increased and then became normal, the rate remained for fifty days between 12 and 26 mm. except for a quick increase to 40 mm. related to the transient use of an unsatisfactory preparation. 2. Rates fell slowly to normal or near normal. Such a response occurred once in each of 3 patients (cases 1, 12 and 15). 3. Rates fell slowly but not to normal. This occurred in 2 cases. In case 2 during each of two courses, of seventy-five and one hundred and forty days' duration, rates were relatively refractory and did not become normal despite marked clinical improvement. In case 19, in which 6.8 Gm. was given within sixty-six days and in which a marked but incomplete clinical effect occurred, sedimentation rates fell from values between 64 and 84 to 32 mm. after fifteen days but varied thereafter between 45 and 60 mm. for the next fifty-one days. In these cases the rates were partially refractory to 100 mg. 4. Rates showed an early slow but fairly marked fall and then a gradual persistent rise. The rates fell to 21 mm. in case 12, to 26 mm. in case 1 and to 42 mm. in case 16; thereafter they rose and remained markedly elevated.

The slowly rising rates which developed in 3 cases (cases 1, 12 and 16) have not been explained. But certain features of hypercortisonism were present in each by the time the rates began to increase after their earlier fall. If hypercortisonism was the cause of the rising rates, one faces a paradox: too much cortisone for certain tissues but not enough to control the rates. The increased rate may have been related to the hypercortisonism which developed in each of these 3 cases. But in Cushing's syndrome sedimentation rates are usually not markedly increased.

Responses of Rates to Repeated Courses.—In most patients given two or more courses rates responded about the same way during each course. There were certain exceptions. Occasionally the rates decreased somewhat faster during the second than during the first course.

Response of Rates to Withdrawal of Cortisone.—When use of cortisone was discontinued, rates usually increased fairly promptly in association with return of rheumatic symptoms and rose to levels at or near those present before cortisone was given. In a few cases rates continued to fall for three to six days after the hormone was withdrawn and then

rose. In 7 cases rates rose immediately (cases 1, 2, 5, 9, 11, 22 and 23). In other cases they remained low for three or four days (cases 3, 7, 13, 15, 20, 21) or even for a week or two.

In some cases rates rose, temporarily at least, to values higher than before (cases 1, 3, 5, 6, 10, 12 and 14). In a few cases rates did not return to precortisone levels within the period of observation. In most cases after use of cortisone rates rose to about the same height that they were before the hormone was given (cases 2, 4, 7 to 12, 14, 20 and 22).

Rates and symptoms often reacted to the withdrawal of cortisone in the same way, at least for the first few days: Symptoms and rates both increased promptly or they remained in abeyance together either for a few days or for as long as two weeks, as in case 6. But in most cases the behavior of rates and symptoms became dissociated soon after cortisone was withdrawn. Rates usually increased much faster than symptoms. Precipitous increases in rates did not indicate precipitous clinical relapses. Sedimentation rates began to increase fairly promptly in cases 7 and 11 and yet prolonged symptomatic remissions occurred. Sedimentation rates did not rise faster in the 2 patients who had rebound relapses than they did in many others whose symptomatic relapses developed slowly.

The postcortisone maintenance of low rates for only a short time probably meant that injected cortisone was still being absorbed from intramuscular deposits. But the few longer delays which occurred may have resulted from a more fundamental mechanism which improved the patient's status for awhile.

EFFECT OF CORTISONE ON HEMOGLOBIN, ERYTHROCYTES AND LEUKOCYTES

Hemoglobin and Erythrocytes.—In 11 of the 23 patients, concentrations of hemoglobin increased during the use of cortisone and/or ACTH. The following cases are representative. One patient (case 23) gained 2 Gm. in twenty days during one course and 4.5 Gm. in thirty-eight days during another course. In 1 case (case 15) the increase was 2.7 Gm. in sixty-four days; in another (case 2) 3 Gm. from two hundred and fifteen days of use of cortisone. In 1 case (case 3) hemoglobin increased 1.4 Gm. during the first (sixty day) course, 1.4 Gm. during the second (eighty-five day) course and 1.9 Gm. during the third (seventy-three day) course. Many of those whose hemoglobin concentration increased during use of cortisone, had decreases when use of the hormone was discontinued.

Hemoglobin concentrations did not increase in the remaining 12 patients; in some cases the duration of administration of cortisone was short. Hemoglobin concentrations of patients usually decreased while they were in the Metabolism Unit on a fixed diet containing about 15 mg. of iron daily.

Erythrocyte counts often increased somewhat, increases generally paralleling those of hemoglobin.

Leukocytes.—A detailed report of the changes noted in the circulating leukocytes and in the bone marrow is in preparation by Drs. J. L. Reynolds and F. J. Heck. Studies of the peripheral blood during prolonged administration of cortisone have shown but few significant changes in the leukocytes. In certain patients an increase in the total number of circulating leukocytes and immature granulocytes and lymphopenia were noted. No consistent change in the number of eosinophils was observed. A statistical analysis of data observed in the entire group showed only a small significant elevation in the total number of circulating leukocytes.

EFFECT OF CORTISONE ON SERUM PROTEINS

In rheumatoid arthritis serum proteins may be normal or abnormal. Serum globulin may be slightly subnormal or normal, but it is often increased, sometimes to the extent that albumin-globulin ratios are reversed. The general effect of cortisone was to reduce the serum globulin; increased concentrations were reduced notably, and normal concentrations were usually reduced slightly. Serum albumin was either not significantly affected or slightly increased. Total proteins were reduced at the expense of globulin, and albumin-globulin ratios were unchanged or slightly increased.

Before cortisone was given, concentrations of serum proteins were abnormal in 3 of the 21 cases. Serum globulin was increased to 3.9, 4.7 and 4.5 Gm. in cases 1, 2 and 15 respectively (normal 2 to 3.6 Gm. per hundred cubic centimeters); total proteins were proportionately increased to 7.9, 8.5 and 8.8 Gm. respectively (normal 6.4 to 7.8 Gm.) and albumin-globulin ratios were slightly inverted. Cortisone caused a normalization of the pattern: Serum globulin and total proteins were reduced, and albumin-globulin ratios were changed in the normal direction. In the remaining 18 of the 21 cases, before cortisone was given values for serum proteins were normal or slightly subnormal. In 10 cases cortisone reduced serum globulin slightly below the limits of normal, to between 1.2 and 1.9 Gm. per hundred cubic centimeters. Serum gamma globulins, said to be measured roughly by zinc sulfate turbidity, decreased during the administration of cortisone.[22a]

EFFECT OF CORTISONE ON CARBOHYDRATE TOLERANCE

In patients with untreated rheumatoid arthritis fasting blood sugar values are normal and glycosuria does not occur. Diabetes coincident with rheumatoid arthritis is rare. Despite this, results of glucose tolerance tests are frequently abnormal in rheumatoid arthritis. This

observation, reported by Pemberton in 1921,[24] has often been confirmed and was the basis of the low carbohydrate diet commonly used for this disease for a decade or more. Such abnormal tests were first interpreted as indicative of impaired carbohydrate metabolism, later as the result of impaired circulation and still later as suggestive of hepatic dysfunction in rheumatoid arthritis. The cause of this abnormality remains unknown.

Very large doses of cortisone or ACTH may induce hyperglycemia and glycosuria in rats.[24c] Cortisone lessens sensitivity to insulin in patients with Addison's disease and intensifies the diabetes of patients with coincident Addison's disease. Obviously, these hormones may in certain doses and under certain conditions impair, temporarily at least, carbohydrate tolerance.

Whatever impairment of carbohydrate tolerance may have resulted from cortisone in our 21 rheumatoid patients was slight. Fasting blood sugar remained normal in all cases.[22a] In none of the patients did significant glycosuria occur. In 9 of the 21 patients glucose tolerance tests were made during the use of cortisone; results were normal in 5 cases and abnormal in 4. In 2 cases (cases 9 and 23) results of sugar tolerance tests were abnormal before cortisone was used but were normal during the use of cortisone, presumably as a consequence of increased intake of carbohydrate. It would appear that in rheumatoid patients without latent or frank diabetes cortisone and ACTH when given in the dose ranges used in our cases do not reduce carbohydrate tolerance significantly. But in rheumatic or nonrheumatic patients with latent or frank diabetes these hormones will probably produce more marked reduction of carbohydrate tolerance. Such an instance recently was reported by Boland and Headley: The daily insulin requirement of a rheumatoid patient with coincidental diabetes was 10 units before cortisone was given and 30 to 50 units during the use of cortisone (1 Gm. in

24. (*a*) Pemberton, R., and Robertson, J. W.: Studies on Arthritis in the Army, Based on Four Hundred Cases: I. Preamble and Statistical Analysis, Arch. Int. Med. **25**:231 (March) 1920. Pemberton, R., and Tompkins, E. H.: Studies on Arthritis in the Army, Based on Four Hundred Cases: II. Observations on the Basal Metabolism, ibid. **25**:241 (March) 1920. Pemberton, R., and Foster, G. L.: Studies on Arthritis in the Army, Based on Four Hundred Cases: III. Studies on the Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, ibid. **25**:243 (March) 1920: Pemberton, R., and Buckman, T. E.: Studies on Arthritis in the Army, Based on Four Hundred Cases: IV. Studies in the Relation of Creatin Metabolism to Arthritis, ibid. **25**:335 (April) 1920. (*b*) Pemberton, R.: Arthritis and Rheumatoid Conditions: Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929, p. 354. (*c*) Ingle, D. J.: Diabetogenic Effect of Some Cortin-like Compounds, Proc. Soc. Exper. Biol. & Med. **44**:176 (May) 1940; (*d*) Production of Glycosuria in Normal Rat by Means of 17-Hydroxy-11-Dehydrocorticosterone, Endocrinology **29**:649 (Oct.) 1941.

eight days). Three days after the use of cortisone was discontinued the insulin requirement was as before, 10 units daily. Wilder [25] currently uses the term "adrenocortical hyperglycemia" to differentiate the condition from permanent diabetes mellitus.

Glycosuria induced by the use of cortisone or ACTH is not necessarily solely diabetic in character; Conn, Lewis and Wheeler [26] have reported evidence which indicates that these hormones depress the renal threshold for glucose. When these hormones have produced significant impairment of carbohydrate tolerance, the effect to date has been reversible.

EFFECT OF CORTISONE ON URINARY EXCRETION OF STEROIDS

Quantitative estimations of 17-ketosteroids and corticosteroids were made by Dr. Harold Mason in several cases before, during and after the use of cortisone.

Urinary 17-Ketosteroids in Arthritic Patients.—The metabolic end products of certain steroids formed by the adrenal cortex and by the gonads are excreted in urine as 17-ketosteroids. At this clinic the normal daily excretion of 17-ketosteroids is considered to be 6 to 20 (average 14) mg. in men and 4 to 17 (average 10) mg. in women. The excretion is low in a variety of conditions, including Addison's disease; it may be increased in Cushing's syndrome, hyperplasia of adrenal glands and carcinoma of adrenal cortex.

Few studies have been made on the excretion of 17-ketosteroids in patients with rheumatoid arthritis. Davison, Koets and Kuzell[27] reported that the daily excretion varied from 3.5 to 21.6 (average 12.8) mg. among 11 females with peripheral rheumatoid arthritis, 19 to 45 (average 29.5) mg. among 4 females with rheumatoid spondylitis and 19.2 to 43.5 (average 26.7) mg. among 31 males with rheumatoid spondylitis. No studies were made on males with peripheral rheumatoid arthritis. Thus the excretion of 17-ketosteroids was essentially normal in females with peripheral rheumatoid arthritis but increased in both males and females with ankylosing spondylitis.

The urinary neutral 17-ketosteroids of 75 arthritic patients were studied by Desmarais.[28] The excretion of 17-ketosteroids was normal in 79 per cent of these 75 patients. But the mean values in 8 patients

25. Wilder, R. M.: Personal communication to the authors.

26. Conn, J. S.; Louis, L. H., and Wheeler, C. E.: Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone: Relation to Uric Acid Metabolism, J. Lab. & Clin. Med. **33**:651 (June) 1948.

27. Davison, R. A.; Koets, P., and Kuzell, W. C.: Excretion of 17-Ketosteroids in Ankylosing Spondylarthritis and in Rheumatoid Arthritis: Preliminary Report, J. Clin. Endocrinol. **7**:201 (March) 1947.

28. Desmarais, M. H. L.: The Neutral 17-Ketosteroids in Rheumatoid Arthritis and Spondylitis, Ann. Rheumat. Dis. **8**:296 (Dec.) 1949.

with spondylitis were low when compared with the findings of Davison and his colleagues. Desmarais suggested that the urinary excretion of 17-ketosteroids might be low in some rheumatoid patients because of the chronicity of their disease, advancing age and the possible presence in adrenal tissues of the same pathologic reactions (panarteritis and granulomas) which have been found in muscles of rheumatoid patients; such lesions might reduce adrenal function.

Among our patients the excretion of 17-ketosteroids per twenty-four hours ranged from 6.4 to 17.6 mg. in males with peripheral rheumatoid arthritis, from 2.4 to 11.9 mg. in similarly affected females and from 3.3 to 17.3 mg. in men with rheumatoid arthritis of the spine and peripheral joints. Of values in all cases 71 per cent were within the normal range; 29 per cent were below this range. The average values in these cases are somewhat higher than those obtained in a small group of cases which we studied in 1945, in which the values were below the average normal though 40 per cent were in the lower range of normal.

Effect of Cortisone.—When the initial concentrations of 17-ketosteroids were subnormal or near the lower limits of normal, the use of cortisone did not cause an immediate decrease in urinary excretions (cases 2 and 3). But when the initial 17-ketosteroid concentrations were normal or above normal, cortisone promptly produced a decreased excretion. Thus in case 1 the daily excretion, which before cortisone was given varied between 5 and 5.5 mg., decreased to 1.5 mg. within six days. In case 21 the excretion dropped within three days to 7 mg. as compared with precortisone excretion of between 14.5 and 17 mg. per twenty-four hours. What happened after this initial reduction in excretion depended on the amount of cortisone being given daily and the length of time it was used.

When 100 mg. of cortisone was given daily for a relatively short time (one to three weeks), the daily excretion increased somewhat after the initial reduction but usually remained less than the precortisone level as long as cortisone was given and for some time thereafter.

If cortisone (100 mg. daily) was given for longer periods (sixty-six days in case 19 and one hundred and eighty-seven days in case 1), after the initial drop in urinary concentration the daily excretion increased to about 4 to 6 mg. and remained at this level for two to three months. Then the amounts excreted decreased to low levels (2 to 3 mg.), and when cortisone was withdrawn the excretion decreased further. In case 1 the value for 17-ketosteroids was 1.7 mg. thirty-seven days after use of cortisone was discontinued.

When daily doses of cortisone were increased from 100 to 200 mg., the daily excretion of 17-ketosteroids increased markedly and even surpassed amounts excreted before cortisone was given. Thus in case 14, in which the precortisone excretion was about 2 to 4 mg. per

twenty-four hours, after 200 mg. of cortisone had been given for about nine days the daily excretion rose to 14 mg.

A tentative interpretation of these results is as follows [29]: The parenteral administration of cortisone apparently promptly depresses adrenal cortex function so that the cortex produces smaller amounts of those steroids (among them cortisone) which are precursors of 17-ketosteroids. Therefore the daily excretion of 17-ketosteroids falls. But the catabolism of the injected cortisone involves the production of small amounts of 17-ketosteroids. As soon as 17-ketosteroids from the catabolism of cortisone begin to be excreted, the total daily excretion increases. If the additive effect from the catabolism of the injected cortisone does not compensate for the suppressive effect (reduced formation of corticosteroids) the daily excretion of 17-ketosteroids, though it increases after the initial reduction, remains below the precortisone level. If the additive effect from the catabolism of cortisone fully compensates for the suppressive effect on the adrenal gland, the daily excretion approximates the precortisone amounts. One of these two situations generally results when daily doses of 100 mg. or less are given. But when large doses (200 mg.) are given daily, the additive effect more than compensates for the suppressive effect and the daily excretion of 17-ketosteroids surpasses the precortisone level, sometimes markedly.

When administration of cortisone is discontinued, the additive effect is removed, and the excretion of 17-ketosteroids (being again dependent largely on the still temporarily depressed adrenal glands) falls.

Corticosteroids.—Corticosteroids are cortisone and other closely related steroids elaborated by the adrenal cortex or certain metabolic modifications of cortisone. In normal urine chemical determination of these compounds may indicate a value much in excess of the amount of cortisone which is present, but in urine after administration of ACTH, cortisone or compound F may constitute a much higher percentage of apparent corticosteroids. At the clinic the normal daily excretion of corticosteroids is considered to be 0.3 to 1.2 (average 0.56) mg. in both men and women.

We know of no previous studies on the excretion of corticosteroids in patients with rheumatoid arthritis. Among our patients the precortisone excretion of corticosteroids ranged from 0.19 to 0.99 mg. in males with peripheral rheumatoid arthritis; 0.29 to 2.11 mg. in similarly affected females, and 0.33 to 1.16 mg. in males with rheumatoid arthritis of the spine and peripheral joints. Although in 2 cases values below normal and in 1 case values above normal were obtained, these patients and all others had one or more determinations in the normal range prior to use of cortisone.

29. Mason, H. L.: Personal communication to the authors.

Effect of Cortisone.—When cortisone was given, the daily urinary excretion of corticosteroids always increased within a few days. The initial increase, which lasted usually only a few days, was greater than the later sustained slight increase. Even so, the maximal daily excretion during administration of cortisone was relatively small in terms of milligrams, rarely over 5 mg. per twenty-four hours. When use of cortisone was discontinued, the rate of excretion gradually returned to precortisone values.

A tentative interpretation [29] follows: Since cortisone, a corticosteroid, was being administered, it was not possible to determine how much of the excreted urinary corticosteroids were from endogenous sources and how much came from the injected cortisone. Part of the increased amounts in urine represented unchanged cortisone, as shown by isolation. Another part probably consisted of metabolites of cortisone which gave the same chemical reactions used for the determination of corticosteroids. The absorption of the initial doses of cortisone is relatively slow—hence the rather slow initial increase in the amounts of urinary corticosteroids. The subsequent reduction in the amounts excreted probably represents an adaptation of the metabolic mechanisms evolved to care for the relatively large amounts of cortisone presented to the body. The extra amounts of corticosteroids which continue to be excreted for several days after injections of cortisone are discontinued probably come from intramuscular depots of cortisone.

OTHER BIOCHEMICAL AND METABOLIC DATA CONCERNING CORTISONE

The metabolic and biochemical studies carried out in these cases by Sprague, Power, Mason, Albert and Mathieson [22a] have been reported with us elsewhere.

From none of these data did we obtain an explanation of the antirheumatic effect of cortisone, nor were they helpful in explaining most of the side effects.

ANTIRHEUMATIC EFFECT OF ACTH

The antirheumatic effect of ACTH was very marked in 4 cases (cases 11, 14, 15 and 18) and marked in 2 cases (cases 6 and 17). The immediate response to ACTH was the same as that to cortisone: a diminution first in stiffness and aching, then in tenderness and swelling. Relief began to appear rapidly, within twelve to thirty-six hours in 4 cases and within two to four days in 2 cases. The maximal initial effect developed within seven to twelve days, by which time symptoms were markedly reduced. When use of ACTH was continued thereafter, greater improvement occurred slowly. Doses of 100 to 105 mg. daily were very effective in cases 6, 11, 14 and 15 but may have been excessive and produced certain transient side effects. In case 18, that of a large

heavy man with very severe arthritis, daily doses of 70 mg. seemed inferior to 100 mg., which was effective and produced no side effects related to ACTH during fairly prolonged administration. Doses of 70 mg. daily were effective in case 17. In case 6 flexions of knees of 30 and 20 degrees respectively disappeared within twelve days and recurred within three weeks after administration of ACTH was discontinued.

NUTRITIONAL EFFECT OF ACTH

Appetite and Weight.—Appetite was increased very markedly in 1 case (case 17) and markedly in 3 cases (cases 6, 15 and 18).

One patient (case 17) gained 2 pounds from eleven days of use of ACTH; another (case 18) gained 13 pounds during the eighty-seven days that he received ACTH.

EUPHOROGENIC EFFECT OF ACTH

Euphoria did not develop among our 6 patients given ACTH, although it commonly developed among our 21 patients given cortisone. This difference was confirmed by those who received courses of each. One patient (case 11) who was euphoric during each of two courses of cortisone, one before and one after the course of ACTH, got from ACTH "no mental lift, no sense of happiness as before." But the difference may have been a matter of relative dosage. Other investigators have reported the development of euphoria in rheumatoid patients who received, as a rule, smaller doses of ACTH than ours did.

CLINICAL PATTERN OF WITHDRAWAL OF ACTH

When ACTH was withdrawn, rheumatic manifestations generally returned within two or three days in the same manner as when use of cortisone was discontinued. Relapses were prompt or fairly prompt in 5 cases, with return of many symptoms within a few days to two weeks. Shortly after the return of symptoms in 2 cases, partial secondary remissions occurred with fairly marked reduction of symptoms for about two weeks (cases 11, 14). One patient (case 18) has retained most of his antirheumatic effect five months after use of ACTH was stopped.

DEVELOPMENT OF SIDE EFFECTS DURING THE USE OF ACTH

Development of side effects during use of ACTH will be discussed later in conjunction with the side effects of cortisone.

EFFECT OF ACTH ON SEDIMENTATION RATES

In general, sedimentation rates decreased promptly and markedly and became normal. In 5 of the 6 cases the rate fell rapidly, indeed precipitously. In the remaining case (case 18) the early doses of 70 mg. daily were inadequate. When larger doses were given daily, the

antirheumatic effect was very satisfactory but the sedimentation rate decreased slowly from 122 to 21 mm. after fifty-nine days of use of ACTH.

When use of ACTH was stopped rates increased quickly with little or no delay (two days at most). Within a few days rates reached values at about the prehormonal level. In 1 of the 2 cases in which secondary clinical remissions occurred there was a leveling off of the rising sedimentation rate (case 11); in the other (case 14) the sedimentation rate, after its initial rise, fell again rather notably.

EFFECT OF ACTH ON HEMOGLOBIN AND LEUKOCYTES

Hemoglobin.—Hemoglobin increased in 1 case (case 15) 1.8 Gm. (from 12.9 to 14.7 Gm.) during 31 days; in another case (case 18) 1.6 Gm. (9.8 to 11.4 Gm.) during eighty-seven days on ACTH.

Leukocytes.—Circulating eosinophils decreased markedly or completely four to six days after ACTH was given and increased within a few days after use of ACTH was discontinued.

EFFECT OF ACTH ON SERUM PROTEINS

The effect of ACTH on serum proteins was similar to that of cortisone. In patients given ACTH, serum proteins were either essentially normal to begin with or had become normal as a result of previous use of cortisone. But in each case serum globulin decreased slightly, as did total proteins; serum albumin was not significantly altered; albumin-globulin ratios increased slightly. In case 18, in which ACTH was given for eighty-seven days, serum globulin fell from 3.3 to 2.1 Gm. and total protein from 6.7 to 6.1 Gm.; the albumin-globulin ratio increased from 1:1 to 1.9:1.

EFFECT OF ACTH ON UTILIZATION OF CARBOHYDRATE

Fasting blood sugar levels remained essentially unchanged. No hyperglycemia developed. No glucose tolerance tests were made in connection with ACTH alone.

EFFECT OF ACTH ON URINARY STEROIDS

17-Ketosteroids.—Injections of ACTH increased promptly and markedly the excretion of 17-ketosteroids in 5 cases studied (cases 6, 11, 14, 17 and 18). Compared with pre-ACTH excretions of 1.8 to 11.7 mg. for twenty-four hours, excretions during use of ACTH rose to amounts varying between 21.1 and 43.8 mg. per twenty-four hours. When use of ACTH was discontinued, the daily excretions decreased rapidly to prehormonal amounts.[29]

Corticosteroids.—Excretion of corticosteroids was also markedly and promptly increased by ACTH. Maximal excretion in 5 cases

studied varied between 3.32 and 17.5 mg. per twenty-hours (cases 6, 11, 14, 17 and 18). The augmented excretion disappeared quickly after ACTH was withdrawn.[29]

EFFECT OF ACTH ON BLOOD ELECTROLYTES

ACTH produced no consistent changes in plasma electrolytes. There was a greater tendency toward a lowering of serum potassium than toward any other alteration. A transient hypopotassemic alkalosis developede in 2 patients (cases 6 and 14) who were given 100 mg. of ACTH daily for twelve days. Other metabolic data are reported elsewhere.[22a]

COMPARATIVE EFFECTS OF CORTISONE AND ACTH

Comparative Dosage.—ACTH and cortisone are not physiologically equal, milligram for milligram. One hundred milligrams of ACTH apparently stimulates the production of more than the equivalent of 100 mg. of cortisone, possibly 200 mg. or even more. Therefore in effect, 100 mg. of ACTH may be as effective as 200 mg. or more of cortisone. This distinction as to relative dosage will explain most of the clinical and biochemical differences now to be mentioned.

Effect on Sedimentation Rates.—Sedimentation rates were less often temporarily refractory to 100 mg. doses of ACTH than to 100 mg. doses of cortisone. The former caused precipitous decreases in rates similar to those from 200 mg. doses of cortisone. Rates increased more promptly after withdrawal of ACTH than after withdrawal of cortisone, perhaps for the following reason: ACTH is more quickly absorbed than is cortisone acetate; continuing absorption of cortisone from incompletely utilized intramuscular deposits may keep the rates down a little longer after use of cortisone than of ACTH. When doses of 100 mg. of cortisone were given, postcortisone sedimentation rates often surpassed precortisone rates. Post-ACTH sedimentation rates usually approximated the pre-ACTH rates. This might be explained thus: Cortisone temporarily depresses adrenal cortex function; ACTH temporarily stimulates this function. When use of either hormone is suddenly discontinued, a state of relative adrenal cortex insufficiency exists for a few days, sometimes for a few weeks. Perhaps after the withdrawal of ACTH the suppression disappears more quickly than after the withdrawal of (equal amounts of) cortisone.

Other Comparisons.—Because it is more rapidly absorbed and metabolized, ACTH must be given oftener (two to four times daily) than cortisone (generally once daily). Certain patients are sensitive to ACTH as a foreign protein. The contamination of ACTH by posterior pituitary substance, though slight, may produce certain annoying symp-

toms. These current disadvantages may in time be removed if a pure product or a physiologically potent fraction of smaller molecular weight, such as may be an outgrowth of the recent work of Li (1948) and of Morris and Morris (1950),[30] can be developed and given in a medium that will retard absorption appropriately.

Responsive Adrenal Glands: An Essential Requirement for ACTH.—Because injected cortisone appears to do all that ACTH does as an antirheumatic agent, one may assume that the pituitary hormone produces its results to the extent that it stimulates the adrenal cortex to produce cortisone or a cortisone-like substance, such as compound F. The adrenal glands of most, but not all, patients with rheumatoid arthritis are responsive to ACTH.[31] But whenever patients like those with Addison's disease have adrenal glands which are not responsive to ACTH, such patients should derive little or no benefit from ACTH though they may be helped by cortisone. Undoubtedly, certain patients with rheumatoid arthritis or another condition will be found to be responsive to injected cortisone but not to ACTH. Three cases of rheumatoid arthritis in which the adrenal glands were unresponsive to ACTH have already been reported.

Theoretic Considerations.—ACTH possesses a certain theoretic advantage and a theoretic disadvantage over cortisone. If the adrenal cortex elaborates not just one hormone (cortisone or the cortisone-like compound F) but several hormones, ACTH may produce effects other than those derived from cortisone; also by stimulating the production of a "physiologically more balanced secretion" than cortisone, ACTH may, at least theoretically, produce fewer side effects. But data at hand do not yet support these assumptions. As a theoretic disadvantage, it has been suggested[32] that the stimulation of adrenal glands by ACTH beyond an optimal point might lead to temporary exhaustion of

30. (*a*) Li.[18] (*b*) Morris, P., and Morris, C. J. O. R.: Isolation of a Polypeptide with High Adrenocorticotrophic Activity, Lancet **1**:117 (Jan. 21) 1950.

31. (*a*) Mach, R. S., cited in Experiments with Pituitary Adrenal Corticotropic Hormone in Rheumatoid Arthritis, Foreign Letters, J. A. M. A. **142**:436 (Feb. 11) 1950. (*b*) Thorn, G. W., and Bayles, T. B.: Pituitary Adrenal Function and Rheumatic Disease, Practitioner **163**:365 (Oct.) 1949. (*c*) Thorn, G. W.; Bayles T. B.; Massell, B. F.; Forsham, P. H.; Hill, S. R., Jr.; Smith, Stephen, III, and Warren, J. E.: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**:529 (Oct. 6) 1949.

32. (*a*) Brøchner-Mortensen, K.; Georg, J.; Hamburger, C.; Snorrason, E.; Sprechler, M.; Videbaek, A., and With, T. K.: The Effects of Adrenocorticotrophic Hormone (ACTH) in a Case of Chronic Rheumatoid Arthritis, Acta endocrinol. **3**:39, 1949. (*b*) Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, Practitioner **163**:393 (Nov.) 1949. (*c*) Selye, H.: Further Studies Concerning the Participation of the Adrenal Cortex in the Pathogenesis of Arthritis, Brit. M. J. **2**:1129 (Nov. 19) 1949.

the adrenal cortex which could be serious in the face of coincident stress. Further experience will determine the likelihood of such a possibility.

Cortisone and ACTH should in no sense be looked on as competitors. It is most fortunate that both are available for correlated and comparative physiologic and clinical studies, from which much useful information will doubtless be obtained.

EFFECTS RELATED TO UNSATISFACTORY PREPARATIONS OF CORTISONE OR ACTH

On rare occasions a short febrile reaction accompanied a given injection of cortisone; the pyrogen has not been identified.

As stated previously (under "Toxicity of ACTH"), despite great effort current preparations of ACTH still contain small contaminating amounts of posterior pituitary substance. This caused mild abdominal cramps, flatus and (occasionally) nausea in 4 of our patients (cases 6, 11, 14 and 15), sometimes after each injection of ACTH. No similar gastrointestinal symptoms developed from cortisone.

A rarer contamination of ACTH was from the pars intermedia. This produced transient pigmentation in case 18.

ACTH derived from pituitary glands of pigs or horses is to man a foreign protein. Fever and hives developed in case 21 after two of five injections of ACTH given to test adrenal function during the use of cortisone. Cortisone, not being a protein, did not produce any such reactions.

SIDE EFFECTS OF CORTISONE AND ACTH

Definition.—Cortisone and ACTH are potent agents capable of affecting many parts of the human economy, many bodily functions and many tissues other than those of joints and muscles. In our previous reports [33] we mentioned the appearance in some cases of mild acne, mild hirsutism, rounding of facial contours, transient edema, irregular menses and, in 1 patient receiving injections for six months, depression. Avoiding the word "treatment," we stated that much more experience would be needed before we would know how effective or safe the prolonged use of cortisone or ACTH would be.

Our experience with these 23 patients has resulted in the further demonstration of a number of effects other than the dominant antirheumatic one. So far as the arthritic patient is concerned, some of these clinical and biochemical effects are desirable: the antirheumatic and antipyretic effects; the nutritional effect, with increased appetite, strength and weight; the "psychic effect," with euphoria and increased mental energy provided it is unaccompanied with nervous irritability or

33. Footnote 1 *a*, *c* and *d*.

other changes in mood; the biochemical effect, which increases hemoglobin and the erythrocyte count and restores the normal ratio of serum proteins.

Other effects which may occur, at least in certain circumstances, are, from the standpoint of the rheumatoid patient, undesirable. To the rheumatoid patient (but not to his physician) some of these effects would be incidental and unimportant—for example, a few striae and mild transient edema. Some might be mildly annoying, such as acne, hirsutism and "nervousness" without other change of mood. Some would be frankly disturbing, as somatic symptoms, transient paresthesias, fatigue and change in mood.

But one cannot group these effects or reactions simply as desirable and undesirable, because what may be desirable in one patient may be undesirable in another. An arthritic patient with latent or frank diabetes would desire a minimal effect from cortisone on his carbohydrate-regulating mechanism, but this same potentiality might be helpful to a nonarthritic patient with spontaneous hypoglycemia.[34] Whether or not the lytic effect of these hormones on lymphoid tissues is useful to patients with rheumatoid arthritis or rheumatic fever, it may be desirable to patients with certain lymphomas or blood dyscrasias.

For these reasons we approve the suggestion that all these physiologic responses to cortisone be considered effects.[22a] They should not be unthinkingly divided into "clinical effects," meaning the desirable ones, and "side effects," meaning the undesirable ones. However, the term "side-effects" is widely used, and its meaning appears to be well understood. Because of this and because the term is currently employed by others investigating cortisone and ACTH in various conditions, we will use it for the present.

General Incidence: Patients With and Without Side Effects.—Of the 23 patients who received cortisone or ACTH or both, 9 (39 per cent) had no significant side effects. In 8 other patients (35 per cent) side effects were mild; in 2 (9 per cent) they were moderate, and in 4 (17 per cent) they were marked.

Of the 9 patients without significant side effects, 8 received cortisone (usually 100 mg. daily) for a total of from twenty-two days to four and one-half months. One (case 18) received ACTH uninterruptedly for eighty-seven days, the average daily dose being 111 mg.

One or the other hormone was given for a total of eleven to two hundred and eighteen days to the 8 patients who had mild side effects. Two of the patients (cases 2 and 3) received cortisone almost continuously for about seven months.

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34. McQuarrie, I.; Bauer, E. G.; Ziegler, M. R., and Wright, W. S.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) in Children with Non-Addisonian Hypoglycemia, Proc. Soc. Exper. Biol. & Med. **71**:555 (Aug.) 1949.

In general, the undesirable side effects of significance developed in patients who received the hormones in what we now believe should be regarded as high doses (200 mg. of cortisone or 100 mg. of ACTH daily) or received smaller doses, usually 100 mg. of cortisone, for relatively long periods. There were exceptions to this generalization. One menopausal woman (case 14) soon began to have side effects on 100 mg. doses, which increased on 200 mg. doses. Another menopausal woman (case 12) did not well tolerate 100 mg. doses given daily for fifty-seven days.

One may conclude, therefore, that although dosage and length of administration were the two chief factors which determined whether or not side effects developed, a factor of individual tolerance also played a role and that men tolerated both hormones better than women, especially menopausal women.

Tentative Grouping.—We have attempted to group side effects in some correlated fashion. The incomplete tentative nature of this grouping is apparent. Part of the grouping indicates the supposed physiologic basis for effects, but, since the causes of many are not yet known, other parts are merely descriptive or anatomic. It may be that some of the effects now listed under group 5 (especially paresthesias) and group 6 will be found to belong more properly under group 1. But further experience is required before a grouping wholly based on physiologic grounds can be constructed.

1. Effect Related to Altered Fluid Balance: The salt-and-water-retaining power of cortisone, though considerably less than that of desoxycorticosterone acetate, was apparent. When significant retention occurred, it usually developed early in the course of hormonal usage. Sometimes some degree of fluid retention persisted as long as the hormones were given, but more frequently initial retention was transient and soon disappeared even though dosage was unchanged. Retention was characterized by polydipsia, oliguria, edema and sudden gains in weight.

Significant polydipsia occurred twice (cases 1 and 10). "Visible edema" was usually transient. Mild pretibial edema developed in 1 man given ACTH. Moderate pretibial edema occurred in 1 case (case 10) when 200 mg. doses of cortisone were given. A sensation of generalized puffiness and stiffness of extremities occurred in 2 cases (cases 1 and 12), in 1 of which marked edema of legs also developed (case 12).

No visible edema developed in 17 patients, including some who received 100 mg. doses of cortisone for sixty-six, one hundred and thirty-three and two hundred and fifteen days (cases 2, 5 and 19), 150 to 200 mg. doses of cortisone for eighteen to thirty-three days, or 70 to 111 mg. of ACTH for eleven to eighty-seven days. In untreated rheumatoid patients transient, sometimes fairly persistent mild or mod-

erate edema, usually pretibial, sometimes of feet or hands not uncommonly develops. Pretibial edema, which was present in 2 cases (cases 3 and 20) before cortisone was given, disappeared during use of the hormone.

Rapid gains and losses of weight, reflecting retention and liberation of fluid, developed in 4 patients given cortisone (cases 1, 7, 10 and 12) and in 1 given ACTH (case 17). In the former cases weight fluctuated only slightly, but in the latter case the patient gained 16½ pounds while receiving ACTH (70 mg. daily) for eleven days and lost 13 pounds within two days after the hormone was withdrawn. Gain due to "invisible edema" was disproportionate to the patient's appetite or intake of food.

Liberation of retained salt and water occurred spontaneously in some cases, or not until doses of the hormones were decreased or discontinued. Spontaneous diuresis, frequent urination, nocturia, output of fluid greater than intake, fluctuating weight or rapid loss of weight (2 to 6 pounds in one to three days) and reduction or disappearance of pretibial edema occurred. Diuresis occurred haphazardly, sometimes early, sometimes late, sometimes several times in the same patient if the hormone was given long enough.

2. Effects Related to Special Deposition of Tissue: Cushing's syndrome produces certain localized thickenings of tissue of the face, neck or trunk which may represent deposits of fat. Effects noted in our cases included (*a*) rounding of the face, (*b*) increased size of the pelvic girdle and (*c*) development of retrocervical fat. When rounding of the face develops to a marked degree, the condition is called "moon-face." "Rounding of the face" occurred in 5 cases (cases 6, 12, 14, 21 and 23) and "moon-face" in 2 cases during the prolonged use of cortisone, for one hundred and sixty-one and one hundred and eighty-seven days respectively (cases 1 and 16). The rounding of the face from cortisone was mild in case 14 but was increased by the use of testosterone. Facial rounding was first noted in a young girl after she had received 2 Gm. of cortisone in about eighteen days; it was first noted in 3 adults (cases 1, 12 and 16) after they had received 3 to 4.7 Gm. within forty to fifty days. No hormonal rounding of the face developed in 16 of the 23 patients, including some who received the hormones for a fairly long time. Increased size of the pelvic girdle made the clothes of 2 women feel tight (cases 1 and 12). Retrocervical fat, or "buffalo hump," developed only in case 12.

3. Effects Presumably Related to Increased Androgenic Activity: These included the appearance of (*a*) acne or (*b*) increased growth of hair either in sites normal for the patient's sex or in sites unusual for the sex (ectopic sites). There was no masculinization or other change in the female voices. Mild acne developed over the shoulders and chest

of 1 patient after he had received 4 Gm. of cortisone in five weeks (case 19). Mild facial acne was present in 2 cases before cortisone was given; in 1 case it increased slightly after 4.2 Gm. of cortisone was given within fifty-two days (case 1); in the other case it did not increase during the first course and disappeared during the second course of cortisone (case 23). No acne developed in the remaining cases.

Growth of hair increased slightly in normal locations (head and face) in 4 men (cases 2, 3, 5 and 10). A light growth of hair on the upper lip and just below the normal hair line of the cheeks developed in case 1 (receiving cortisone daily for one hundred and eighty-seven days), and in case 14 (three short courses of cortisone, generally 200 mg. daily). In no case was hirsutism marked, and the women did not grow "beards."

4. Effects Which Concerned Libido or Menstruation: These included transient diminution of libido or potentia, irregular menstruation and amenorrhea.

Specific inquiry concerning libido and potentia was made of only 8 of the 13 men. Five noted no lessening of sexual interest (cases 2, 3, 5, 8 and 22); indeed, 1 thought libido increased; the other 3 noted transient diminution of sexual interest. One patient noted decrease in libido but not potentia during his second and third courses of cortisone. One (case 10) while receiving 200 mg. daily noted a decrease in libido and potentia but no decreased satisfaction. Another (case 15) noted less sexual interest during a sixty-four day course of cortisone, 100 to 150 mg. daily, and also during a thirty-one day course of ACTH, 75 to 100 mg. daily; within a week after use of ACTH was discontinued sexual relations were normal.

The cause of the diminished sexual interest in 3 of the 8 men is not entirely clear. It may be assumed that it was hormonally induced, since diminished libido and potentia may occur in Cushing's syndrome. Further studies are required.

Do these hormones affect menstrual function? Of the 11 women, 5 were menopausal. In 4 of the 6 nonmenopausal women (cases 6, 9, 11 and 13) menstruation was not affected by cortisone, ACTH or compound F. One of these women (case 13) had been trying for three years to become pregnant. She received 3.7 Gm. of cortisone in twenty-nine days; seven weeks later she became pregnant. The only rheumatoid patient whose menses were apparently disturbed by cortisone received the hormone for one hundred and eighty-seven days (case 1).

Does the menopause influence the utilization of these hormones? Three of the 5 menopausal women obtained from cortisone very marked relief from the arthritis with minimal or no undesirable effects (cases 7, 20 and 21). But the other 2 had disturbing side effects although joints were markedly relieved: One, a 43 year old woman, was just

entering the menopause and had marked symptoms thereof (case 12); the other, a 45 year old woman (case 14) had had artificial menopause four years previously. In the latter disturbing symptoms developed from ACTH and cortisone which the use of estrone and especially testosterone coincident with cortisone partially prevented.

The interrelationship of rheumatoid arthritis, menstrual function and utilization of cortisone needs further study. Rheumatologists have long suspected some connection between the disease and disturbed menstrual function. The disease affects females two or three times as often as males, often appears in association with some "menstrual crises," such as puberty or menopause, is made worse by menses and relieved by pregnancy and often reappears or occurs for the first time during puerperium. Not uncommonly menstruation becomes irregular after the onset of rheumatoid arthritis (case 23). Are premenstrual flare-ups occasioned by a temporary depletion of cortisone or a disturbed utilization or augmented need at that particular time?

The occurrence of amenorrhea after relatively short courses of cortisone or ACTH given to 3 adolescent girls with acute rheumatic fever has been reported elsewhere.[34a] Apparently menstrual function of adolescents may be more easily disturbed by these hormones than that of adults. Our data do not indicate that the menstrual irregularity, coincident with the use of these hormones, results from disturbed gonadotropic function.

5. Effects Related to the Nervous System: Some of the symptoms related to the nervous system were desirable; others were undesirable. The desirable effects (euphoria and increased cerebral activity with increased mental and physical energy) have been discussed. The desirable and undesirable effects (euphoria, nervousness, variability in mood or psyche and paresthesias) seemed to be gradients of a single process. Although some patients experienced only one, in others a second effect replaced the first or in time accompanied it. When a single change of mood occurred, it was oftener in the direction of euphoria than of nervousness or depression. All changes in mood were transient, sometimes very transient, appearing only part of a day or for a day or two and then disappearing, perhaps to reappear again or to remain absent. All disappeared rather quickly during or after the use of the hormones. The presence or absence of these changes in mood seemed to bear a general relationship to dosage and duration of administration of the hormones, but a factor of individual susceptibility was also evident.

Nervous Tension. This was described as "nervousness," "restlessness" or "irritability," occasionally as "butterflies in the stomach." Mild restlessness developed in a number of cases, sometimes early, sometimes late; it developed in 2 cases (cases 6 and 11) after five and seven days

34a. Footnotes 1*b* and 22*a*.

of use of ACTH; in 1 case (case 14) it developed after thirty-seven days of use of cortisone. Patients said "I must keep doing something" or "I have so much energy I think I will explode." This nervous tension was sometimes translated into purposeless activity, in contract to the purposeful activity of patients in the euphoric phase. We noted three degrees or grades of this effect: Grade 1. There were mild swings in mood; the patient felt "up" certain hours of the day, "down" other hours, and often tried to correlate the changes in mood with the number of hours which had elapsed since his last (daily or semidaily) injection. Grade 2. Swings in mood were more marked. Three patients noted this. They were euphoric part of the day and somewhat depressed or "weepy" part of the day (cases 12, 14 and 15). They noted "mental fuzziness" or poor mental concentration, increased physical energy some hours and at other times increased fatigue, lassitude or weakness. On occasion this effect was related to a transient reduction of serum potassium, but usually it was not. Energy alternating with fatigue developed early in 1 case (case 14), after 2 Gm. of cortisone had been given within nineteen days, and late in another case (case 1), not until cortisone had been given for three and a half months. Grade 3. Mood variability of this grade involved marked change. It affected only our first patient, who received cortisone continually for one hundred and eighty-seven days. During six months of use of cortisone this patient progressed from euphoria to simple nervousness and then through alternating changes of mood to depression. During the first three months euphoria was dominant; thereafter nervousness and later depression were dominant. The depression was persistent on some days and interrupted by "spikes" of euphoria on other days. After use of cortisone was discontinued, the depression and other signs of hypercortisonism regressed but severe arthritis returned.

No nervousness was experienced by 17 of the 23 patients, some of whom received cortisone or ACTH for fairly long periods. Of the 14 euphoric patients, 9 had no associated nervousness. But nervous tension accompanied or followed euphoria in 5 cases. Nervousness developed in 1 case (case 6), from ACTH but not from two courses of cortisone; in another case (case 11), from both ACTH and cortisone.

Electroencephalographic studies were made in 7 cases. Results will be reported by Drs. Braceland and Rome.

No paresthesias developed in 19 of the 23 patients. The only paresthesia noted by 1 patient was occasional "burning sensation" over a knee (case 15). One of the 2 menopausal women who tolerated cortisone poorly noted transient retrobulbar pressure and bone pain in arms and legs (case 12); the other noted bone pain and tingling of fingers (case 14). A variety of paresthesias, including transient burning sensations over a joint or an extremity or of buttocks, tingling of fingers

(these two sensations were an immediate precursor of diuresis resulting from spontaneous liberation of retained fluid), flashes of skeletal pain, bone pain (a deep ache in arms and legs, "not in joints" and not relieved by heat), ocular tension, bandlike pain about the thighs and pulling sensations affecting the nose or skull, developed in case 1.

6. Miscellaneous Effects: These included the development of striae or a number of somatic complaints which resembled functional symptoms of psychoneurosis.

Newly developing reddish striae over thighs occurred in only 1 of the 23 rheumatoid patients, the youngest, a girl aged 17 (case 23). They were noted after she had received 100 mg. of cortisone daily for eighteen days. Such striae developed in 4 adolescents with rheumatic fever given large doses of cortisone. Apparently such striae are more likely to develop in young persons, especially young girls, than in adults. Such striae must be differentiated from old white striae distensae often found in women and related to previous pregnancies and sometimes present in men.

Ten of the 23 patients experienced sometimes only one, sometimes more than one, of the following somatic symptoms during the use of cortisone or ACTH. Transient headaches developed in 5 cases: after two and eleven days of use of ACTH (cases 11 and 17); after seventeen days (total dose 1.9 Gm.) and sixty-five days (total dose 9.3 Gm.) of use of cortisone (cases 10 and 12). In 2 of these cases headaches did not recur when estrone or testosterone was given coincidentally with cortisone (cases 12 and 14). Fulness or heaviness in the head developed in 3 (cases 1, 11 and 14). Transient dizziness or lightheadedness occurred in 5 (cases 1, 2, 11, 14 and 17): after about 700 mg. of ACTH in cases 11 and 17, and after 3 to 4 Gm. of cortisone in cases 1 and 2. Tinnitus was noted in case 1 after administration of 3.4 Gm. of cortisone in forty-four days, in case 10 after 9.3 Gm. of cortisone in sixty-one days. Transient blurring of vision developed irregularly in 6 (cases 1, 2, 10, 12, 14 and 15): after use of about 1.5 Gm. of cortisone in sixteen days in 2 (cases 2 and 14); after use of about 3.2 Gm. during thirty days in 2 (cases 12 and 15) and after use of about 9 Gm. within sixty-five and one hundred and two days in 2 (cases 1 and 10). In 1 case (case 15) it developed when doses of cortisone were increased from 100 to 150 mg. daily. Heaviness, fulness or "soreness" over the chest or sternum also occurred irregularly in 4 (cases 1, 6, 12 and 14): after five or six days of use of ACTH in 2 and after seventeen days in 1 and after five months of use of cortisone in 1. Precordial symptoms (pounding, palpitation) occurred in 2 (cases 1 and 12), transient symptoms (globus, fulness, tightness) involving the neck in 2 (cases 12 and 18) and spells of nonmenopausal sweating in 1 (case 5).

Weakness, Fatigue, Exhaustion. These are among the main symptoms of rheumatoid arthritis. They were experienced in varying degrees by most of our patients before the hormones were given and often recurred after or between courses of either cortisone or ACTH. Muscular weakness is also a feature of Cushing's syndrome.

In 7 of our 23 patients these symptoms developed transiently during the use of the hormones. At times it was difficult, if not impossible, to determine whether the weakness and lassitude were solely of rheumatic origin or were hormonally induced; when exhaustion seemed out of proportion to the arthritic activity present we considered that it was probably related to the hormones. When muscular weakness and exhaustion occurred, they developed fairly soon in some cases and late in others. Reduction of serum potassium was not a factor in some cases (cases 1, 11, 12 and 16) but may have been a factor in others (cases 6, 14, 15). Individual tolerance (cases 12 and 14) played a role, as well as dosage and length of administration. One patient (case 12) had these symptoms while receiving cortisone but not later when estrone was given with cortisone.

Effect on Blood Pressure. In rheumatoid arthritis the blood pressure is usually in a low range of normal or even subnormal for the patient's age. There was no significant increase of blood pressure in any case. In 1 prematurely senile patient (case 16) the blood pressure varied widely (systolic between 110 and 160 mm. and diastolic between 60 and 90 mm.); this apparently was unrelated to the use of cortisone.

In 3 patients (cases 6, 11 and 14) the blood pressure remained unchanged when 100 mg. of cortisone was given daily; systolic pressures rose slightly, 10 to 30 mm., when 200 mg. of cortisone was given daily. In 1 of the same 3 cases (case 11) during the use of ACTH the systolic blood pressure was unchanged, in another (case 14) increased 10 to 20 mm. and in the third (case 6) increased 20 to 40 mm. But in no case were these increases beyond the upper limits of normal for the patients' ages, and in no case did the diastolic pressures increase significantly.

7. Withdrawal Phenomena: In most cases the discontinuance of use of these hormones was not followed by any unexpected phenomena, merely the return of articular and constitutional features of the disease. Sometimes there were slight lags in the development or resolution of certain phenomena related to the use of the hormones. Retention of salt and water, when it occurred, usually developed early and then disappeared well before the end of a course; but sometimes symptoms and biochemical alterations related to sudden shifts of fluid and electrolyte balance lagged correspondingly and were still present or developed shortly after withdrawal of the hormones.

Five features listed in order of appearance might be regarded as withdrawal phenomena: (1) posthormonal liberation of fluid and electrolytes with or without attendant symptoms of significance; (2) rebound relapses; (3) secondary spontaneous remissions developing shortly after the posthormonal relapse; (4) transient posthormonal weakness, and (5) transient posthormonal thinning of hair.

Posthormonal liberation of fluid and electrolytes produced dehydration and notable gastrointestinal and other symptoms in 1 case (case 17) for a few days. Rebound relapses occurred in 2 cases (cases 8 and 9), in which there was a prompt and severe return of some but not of other rheumatic manifestations. Secondary spontaneous remissions have already been discussed.

Posthormonal muscular weakness and exhaustion affected 14 patients, men and women alike: In 4 (cases 1, 12, 14 and 16) it was a prolongation of the weakness and lassitude which developed during the use of cortisone or ACTH; in 8 it developed after the use of hormones (cases 2, 3, 4, 5, 10, 15, 19 and 21). It usually came on two or three weeks after withdrawal of hormones, varied in severity, lasted a few weeks (sometimes three to four, occasionally longer) and then disappeared.

Thinning of Hair. In contrast to the stimulation of growth of hair which occurred in a few cases during the use of the hormones, 4 patients who had received cortisone in 100 mg. doses for a fairly long time (cases 1 and 3) or 200 mg. doses for a shorter time (cases 10 and 12) noted later some thinning of hair. In cases 1 and 12 the retarded growth was not noticed until two and three months after the use of cortisone was discontinued. In case 10 it was noted after the first course (or rather, because of a lag, during the second course); in case 3 the "hair seemed finer" after each of two courses. The condition was of no cosmetic significance; normal growth of hair soon occurred.

Appearing Time of Side Effects.—There was no characteristic pattern for the development of side effects. The first symptom was noted in some cases between the twelfth and the eighteenth day of use of cortisone and varied from palpitation and heaviness in chest in 1 case (case 12) to restlessness in another (case 14) and appearance of red striae in another (case 23). Other patients noted none of these symptoms until after four to six weeks of use of cortisone: In 1 case the first symptom was transient blurring of vision with variability in mood (case 15); in another, mild acne (case 19); in 1, rounding of the face (case 16); in 1 (case 2), transient dizziness and restlessness, and in another (case 1), early rounding of the face with mild dizziness.

Those who noted early one or another of these symptoms had received from 1.4 to 2 Gm. of cortisone within twelve to eighteen days. In the latter instances 3 to 5 Gm. had been given within four to six weeks.

When ACTH was given (in doses of 100 mg. daily) symptoms, if they appeared, occurred earlier, within the first few days in 3 cases: heaviness of the chest, headache, restlessness, dizziness or fatigue.

Interpretation of Symptoms.—What physiologic reaction produces the antirheumatic effect? What physiologic responses or aberrations produce the side effects, and can they be counteracted without interfering with the antirheumatic effect? Why did side effects develop early in a few, later in some and not at all in many of our patients? These questions we have tried to answer by attempting to correlate results of many biochemical tests and clinical changes with the development of the antirheumatic and other effects. But this difficult task has not yet given satisfactory results. Further discussion now is inappropriate.

EFFECTS OF CORTISONE AND ACTH ON SYNOVIAL HISTOPATHOLOGIC CHANGES

Articular biopsies of synovia of the knee were carried out in 7 cases (cases 6, 10, 15, 16, 18, 21 and 23) before and at various times during the use of cortisone or ACTH or both. In each case synovial inflammation appears to have been reduced by these hormones. Histopathologic improvement was mild, moderate or marked depending on how long the hormones had been given and on the patient's individual response to them. Sometimes the reduction of inflammation was mild or moderate, especially when the use of the hormones had been relatively short. In case 16, in which the least satisfactory clinical response developed, the histologic improvement was not marked despite administration of cortisone for many weeks. In 4 cases the synovial inflammation was markedly reduced, so that the histopathologic picture, though not normal, was much improved.

Histologic improvement was indicated by reduction in the cellular reaction with a decreased number of plasma cells and lymphocytes, reduction of papillary tufting, reduction or absence of deposition of fibrin and lessened necrosis and edema. Further studies will be reported with Dr. M. B. Dockerty, of the Division of Surgical Pathology.

Delayed healing of wounds in 2 patients with severe lupus erythematosus given ACTH was reported by Ragan, Grokoest and Boots. Some of our biopsies were needle biopsies; specimens from others were obtained by arthrotomy. No difficulty in healing was noted in these cases.

SUMMARY OF RESULTS FROM RELATED COMPOUNDS AND OTHER STEROIDS ON RHEUMATOID ARTHRITIS

Compound A.—Compound A of Kendall (11-dehydrocorticosterone) was given to 3 patients, 100 mg. intramuscularly daily for seven, nine and fourteen days respectively (cases 6, 3 and 13). No significant effect on joints or on sedimentation rates was obtained from these doses.

Compound F.—Compound F of Kendall (17-hydroxycorticosterone) (not the acetate) was given intramuscularly in case 6, 900 mg. within twelve days. Joints improved, and the sedimentation rate decreased markedly before our meager supply was exhausted.

Several other steroids were given at various times to the patients; the comparative effects will be reported elsewhere.

RESULTS OF OTHERS WITH CORTISONE, ACTH IN RHEUMATOID ARTHRITIS

Cortisone.—Preliminary results with cortisone given for only a few days to a total of 9 patients with severe or moderately severe rheumatoid arthritis or spondylitis were reported by Bauer, Boland, Freyberg, Holbrook and Rosenberg [35] before the Seventh International Congress on Rheumatic Diseases. In each case marked improvement occurred. In Boland's 2 cases electrophoretic studies of serum proteins revealed that alpha and beta globulin, especially the mucoprotein M_1 fraction, were abnormally increased before cortisone was given and decreased during use of the hormone.

In 5 severe and 3 less severe cases of rheumatoid arthritis, cortisone was given by Boland and Headley.[36] In the 5 severe cases a total of 1 Gm. was given within eight days. Immediate results were "decidedly pronounced improvement" in 3, "pronounced improvement" in 1 and "moderate improvement" in 1. Euphoria developed in 3 patients, 1 of whom became almost hypomanic. In encephalograms, made in 2 cases, the frequency of alpha waves increased 8.8 and 9.2 per cent during the use of cortisone, suggesting increased cerebral activity. After the short courses were completed, relapses developed promptly in 4 of these 5 patients. But 1 patient, after a five day relapse, had a secondary spontaneous partial remission which continued two months; she regained "75 per cent" of the initial improvement, and the sedimentation rate decreased markedly.

Three other patients of Boland and Headley, 2 with moderate and 1 with mild rheumatoid arthritis, were given smaller doses, only 50 mg. daily for ten to fifteen days; clinical manifestations were "adequately but not completely controlled." Thereafter doses of 50 mg. were given every other day for twenty-one days; these doses were "not as effective."

ACTH.—Results of ACTH in a total of 42 patients with severe or moderately severe rheumatoid arthritis, which in several cases had lasted

35. Bauer, W.; Boland, E. W.; Freyberg, R. H.; Holbrook, W. P., and Rosenberg, E. F.; in the Proceedings the Seventh International Congress on Rheumatic Diseases, New York, May 31, 1949, to be published.

36. Boland, E. W., and Headley, N. E.: Effects of Cortisone Acetate on Rheumatoid Arthritis, J. A. M. A. **141**:301 (Oct. 1) 1949.

ten to twenty-eight years, have been reported.[37] Armour's preparation was used by American workers; that of Organon Company, by Scandinavian investigators. Satisfactory results were obtained in all but 6 cases: The adrenal glands of 3 patients were not responsive to ACTH as predicted by use of the Thorn test,[38] and two early European preparations were presumed to have been inactive in 3 cases.[37b, l] The pituitary hormone was given for only one to three weeks in most cases, for many weeks in a few cases. Dosage varied considerably; initial daily doses were from 40 to 100 mg.; usually after a few days, doses were gradually decreased. Small "maintenance" doses (6.25 to 20 mg. daily) were given to a few patients for several weeks. Doses were generally given in divided amounts, at first every six hours and later every eight or twelve hours. But to 1 patient who responded very well a single daily dose was given.[32a]

Flexion contractures and subcutaneous rheumatoid nodules decreased. Euphoria developed in most cases but was occasionally less in the second than in the first course. Electroencephalograms revealed increasing amounts of slow (5 per second) activity. One patient's euphoria briefly

37. (*a*) Spies, T. D., and Stone, R. E.: Relief of the Symptoms of Acute Gout and Rheumatoid Arthritis by Means of Pituitary Adrenocorticotropic Hormone (ACTH), South. M. J. **42**:720 (Aug.) 1949. (*b*) Jonsson, E.; Berglund, K.; Hävermark, N. G.; Nyström, G., and Paulsen, F.: Endokrinologiska synpunkter på vissa reumatiska och andra mesenkymala sjukdomstillstand, Svenska läk.-tidning. **46**:1921 (Sept. 16) 1949. (*c*) Footnote.[31b, e] (*d*) Markson, D. E.: Prolonged Treatment of Rheumatoid Arthritis with Pituitary Adrenocorticotropic Hormone (ACTH), J. A. M. A. **141**:458 (Oct. 15) 1949. (*e*) Brøchner-Mortensen, K.; Georg, J.; Hamburger, C.; Snorrason, E.; Sprechler, M.; Videbaek, A., and With, O. T. K.: Hormonbehandling af polyarthritis chronica, Ugesk. f. læger, **112**:1255, 1949. (*f*) Brøchner-Mortensen and others.[32a] (*g*) Spies, T. D.; Stone, R. E.: Dreizen, S., and Morton, B. F.: Further Studies With Pituitary Adrenocorticotropic Hormone (ACTH), South. M. J. **42**:991 (Nov.) 1949. (*h*) Ragan, C.; Grokoest, A. W., and Boots, R. H.: Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **7**:741 (Dec.) 1949. (*i*) Edström, G.: Undersökningar över vissa hormoneffekter vid kronisk artrit (ACTH) hypofysinplantation, via adrenalinretning, DOCA, progestin, testosteron, Svenska läk.-tidning. **46**:2697 (Dec. 16) 1949. (*j*) Hävermark, N. G., and Nordenson, N. G.: Hematologiska förändringar hos ett fall av reumatoid artrit behandlat med adrenocorticotropt hormon (ACTH, corticotropin), ibid. **46**:2713 (Dec. 16) 1949. (*k*) Elkinton, J. R.; Hunt, A. D., Jr.; Godfrey, L.; McCrory, W. W.; Rogerson, A. G., and Stokes, J., Jr.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **141**:1273 (Dec. 31) 1949. (*l*) Footnote 31*a*.

38. (*a*) Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: The Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005 (July 17) 1948. (*b*) Footnote 31*a*.

"developed into a mania" which was terminated by electroshock therapy; curiously, this patient maintained the antirheumatic effect of ACTH for at least twenty-five days after use of the hormone was discontinued, longer than any other patient in that series. Transient mild hyperglycemia and glycosuria occurred in only 1 case. Euglobulin and gamma globulin were reduced. Antistreptolysin decreased or remained unchanged. Agglutinins for sensitized sheep cells diminished slightly. The heart size increased 1.9 and 2 cm. in 2 patients; during a second course the heart size increased only 0.5 cm. in 1 of these patients whose sodium intake was restricted. Serum potassium decreased in 1 case to 2.7 milliequivalents per liter; no symptoms accompanied reduction of serum potassium, which was controlled by administration of 1.8 Gm. of potassium chloride daily. Detailed hematologic studies in 1 case were reported.

When use of ACTH was discontinued, relapses occurred fairly promptly. The effect was maintained longer in milder cases; in many cases relapses were not complete; in 2 cases prolonged remissions were reported. Rebound relapses occurred occasionally as did secondary partial remissions.

ACTH Peptides.—A patient who was given Li's ACTH peptides, 13 mg. daily for four days, responded quickly, within three to four hours after the initial injection of 2 mg. He also responded twice to pure ACTH protein, 25 mg. daily for four days and later 13 mg. daily for four days.[39]

APPLICATION OF CORTISONE AND ACTH TO OTHER ARTICULAR CONDITIONS

When we observed the suppressive effect of cortisone and ACTH on rheumatoid arthritis, certain conjectures arose at once. Could rheumatoid arthritis be not a disease per se but a syndrome produced by any factor which causes a relative deficiency of adrenal hormone? Do some of the nonmicrobic arthritides usually considered "specific" (such as arthritis of lupus erythematosus disseminatus, of psoriasis, of chronic ulcerative colitis or even of acute gout and rheumatic fever) represent likewise a transient deficiency of adrenal hormone? Are these arthritides merely "adrenal complications" of different parent diseases? In other words, regardless of the distinctive parent diseases, are some of these articular complications identical with "rheumatoid arthritis"?

With such ideas in mind we administered these hormones in a few cases of acute rheumatic fever, severe lupus erythematosus dissemi-

39. Luft, R.; Sjøgren, B., and Li, C. H.: Results of Administration of Adrenocorticotrophically Active Peptides (ACTH Peptides) to a Patient Suffering from Rheumatoid Arthritis, Acta endocrinol. **3**:299 (Dec.) 1949.

natus with or without polyarthritis, psoriasis with polyarthritis, chronic ulcerative colitis with polyarthritis, tuberculous arthritis and osteoarthritis.

EFFECT OF CORTISONE AND ACTH ON ACUTE RHEUMATIC FEVER

Our Studies.—Of the additional considerations which suggested that these hormones might favorably influence acute rheumatic fever, two were fairly impressive and two were merely suggestive. 1. Rheumatic fever bears a close relation to rheumatoid arthritis, according to many rheumatologists. 2. Cardiac muscle and fibrous tissue of heart valves are not very different from the skeletal muscle and fibrous tissues which are so promptly benefited in rheumatoid arthritis. 3. Intercurrent jaundice may have acted favorably in 1 or 2 cases of acute rheumatic fever.[3d] 4. The development of acute rheumatic fever during pregnancy appears to be rare.

Since March 28, 1949 we have given cortisone to 7 patients with acute rheumatic fever and ACTH to 4 more; we have also given cortisone to 2 patients with severe rheumatic carditis and cardiac failure. Early daily doses of cortisone were usually 200 mg., later 100 mg.; total doses were 3.45 to 5.2 Gm. within twenty-two to forty days. Initial daily doses of ACTH were 25 to 60 mg., usually 45; later doses decreased to 10 to 15 mg. daily. Total doses were about 400 to 825 mg. within sixteen to thirty-eight days. Doses varied somewhat depending on the age and size of the patient.

Results on the acute phase in 8 of these cases have been reported.[40] Fever disappeared within one to six days; acute polyarthritis, within two to eleven days. The rapid sedimentation rates became normal within twelve to twenty days in 7 cases and more slowly in the eighth. Hyperglobulinemia was reduced, and albumin-globulin ratios became normal. Hemoglobin increased from 1.1 to 2.4 Gm. within eleven to twenty-two days. Tachycardia disappeared within one to four days and was sometimes replaced by bradycardia, which disappeared when the dosages were reduced or discontinued. P-R intervals, which were increased in 5 cases, became normal within one to eleven days in 4 cases and decreased from 0.26 to 0.22 second in 1 case, in which irreversible changes may have resulted from previous attacks of carditis. Side effects (rounding

40. (*a*) Hench, Slocumb, Barnes, Smith, Polley and Kendall.[3b] (*b*) Barnes, A. R. and Smith, H. L.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Cortisone) and of Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatic Fever, unpublished data. (*c*) Barnes, A. R., and Smith, H. L.: The Effects of the Administration of Cortisone and ACTH on Patients with Acute Rheumatic Fever, Mod. Concepts Cardiovas. Dis. **19**:59-60 (Feb.) 1950.

of face, striae, acne, amenorrhea) sometimes occurred but usually disappeared after use of the hormones had been discontinued for several weeks.

About two to six weeks after use of the hormones was discontinued, short mild rheumatic recurrences appeared in 3 of the 8 cases but disappeared when the hormones were again given and did not return. Optimal dosage and duration of administration remain to be established. It is probable that we gave doses higher than necessary.

Reexaminations of the hearts were made eight to ten months after use of the hormones was stopped. To date we have found no definite evidence of new, or increased old, rheumatic carditis. Although acute manifestations of rheumatic fever were quickly abolished, it will take months or years to determine whether cortisone or ACTH will prevent the initial development or aggravation of rheumatic carditis.

Experience of Others.—In 3 cases of acute rheumatic fever 30 to 40 mg. of ACTH was given daily for eight to fourteen days by Thorn and others [21b, c] with results similar to ours. Acute manifestations, which included pericarditis and gallop rhythm, rapidly disappeared.

CORTISONE AND ACTH IN LUPUS ERYTHEMATOSUS DISSEMINATUS

Our Experience.—With our colleague Dr. L. A. Brunsting we have given cortisone or ACTH to 6 patients with severe disseminated lupus erythematosus with or without polyarthritis. The first patient, who was very ill and had previously had renal involvement, received cortisone, usually 100 mg. daily, continuously for one hundred and sixty-six days (February 25 to Aug. 9, 1949). Arthritis, pericarditis, pleurisy and leukopenia disappeared; the Hargraves phenomenon, "lupus erythematosus cells" in sternal bone marrow, was no longer evident. Albuminuria persisted. The blood pressure increased notably in this case after daily doses were increased to 150 mg. The sedimentation rate decreased, and the patient's general condition improved greatly. Rounding of the face and striae but no impairment of carbohydrate utilization developed. When use of the hormone was discontinued, mild relapse involving muscles and joints developed within six weeks, but in January 1950 she was still much better and able to do much of her housework.

Further details will be reported with Dr. Brunsting. These hormones appear to be helpful, perhaps even life saving, in acute crises. Temporary remissions were induced, not cures.

Experience of Others.—Essentially similar results from ACTH were noted in 3 cases studied by Thorn and co-workers.[21b, c] In 2 severe cases ACTH was given by Ragan, Grokoest and Boots [27h]: A symptomatic remission resulted in 1 case. In the other a severe exacerbation, complicated by decubitus ulcers, developed post partum. The patient responded

well to ACTH but died of pulmonary infarction. Of 2 critically ill patients given ACTH by Elkinton and colleagues,[37k] one obtained a remission; the other responded initially, then became refractory even to larger doses and died.

CORTISONE AND ACTH IN PSORIASIS AND PSORIATIC ARTHRITIS

Our Experience.—One patient with severe psoriasis from head to foot and moderately severe psoriatic arthritis received cortisone, 100 mg. daily for forty-three days (May 21 to July 2); later, 3.5 Gm. of ACTH within twenty-eight days. During each course her arthritis disappeared promptly, but the psoriasis improved slowly. Remissions, not cures, were induced. Details will be reported with Dr. Brunsting. In considering this somewhat dissociated response of lesions of skin and joints to these hormones, one should recall the reported effects of jaundice or pregnancy on arthritis associated with psoriasis: In some cases jaundice or pregnancy relieved joints but not skin; in other cases pregnancy relieved psoriasis unassociated with arthritis.

EFFECT OF CORTISONE ON TUBERCULOUS ARTHRITIS

It seemed important to determine to what extent, if any, cortisone or ACTH might affect arthritis of proved bacterial origin. We suspected that these hormones might influence some "nonspecific" part of the clinical pathologic picture but might fail to influence the "specific" part. Two patients with tuberculous monarthritis of a knee received cortisone. In each case the tuberculous nature of the arthritis was confirmed by articular biopsy, synovial culture and guinea pig tests. The first patient received two courses of cortisone, 100 mg. daily. During the first course (thirty days) the stiffness, tenderness and soreness on motion of the knee disappeared. The sedimentation rate rose first from 40 to 78 mm. and then fell to normal, 15 mm. Articular swelling decreased, but thickening persisted. Results of articular biopsy, guinea pig test and cultures remained positive. Although the knee was essentially symptomless, the patient still had tuberculous arthritis from the pathologic and bacteriologic standpoint. Between courses his articular symptoms returned. He responded similarly to a second course for thirty-one days.

The response in the second case was the same as in the first. Our tentative conclusion is that cortisone controlled the hyperergic tissue reaction but did not exert a bacteriostatic or bactericidal effect. Reactions to tuberculin tests remained positive. Neither of these patients had active pulmonary tuberculosis, and there was no evidence that the disease was influenced unfavorably.

The use of these hormones in cases of tuberculosis should be investigated with caution. Studies now being made in animals by our colleagues

in the Division of Experimental Medicine suggest that cortisone may neutralize the beneficial effect of streptomycin, retard fibrosis and reverse positive tuberculin reactions in experimental tuberculosis of guinea pigs.[41]

EFFECT OF CORTISONE ON OSTEOARTHRITIS

Although some rheumatologists still regard osteoarthritis as closely related to rheumatoid arthritis, the majority consider them different pathogenetically. The effect of jaundice on osteoarthritis is not clear-cut.[41a] Our experience with cortisone concerns only 1 case.

A 69 year old rancher noted enlarged lymph nodes and numerous bullae of the skin in January 1949. At the clinic in September a diagnosis of chronic lymphatic leukemia was made. The leukocyte count was 84,000, with lymphocytes 81 per cent. Biopsy revealed leukemia cutis. Fifteen years previously transient painful stiffness had developed in the patient's left knee and had progressed since. There was no related trauma. For several years he had had pain when mounting a horse, and daily stiffness so that he could not cross his knees. The knee was not swollen or tender but creaked considerably. There was no locking. Roentgenograms revealed osteoarthritic changes of the left knee with a narrowed joint space. The sedimentation rate was normal, 9 mm. The diagnosis was primary osteoarthritis.

Because of the leukemia, cortisone was given by our hematologists for a total dose of 2 Gm. within eighteen days (September 13 to 30). The skin improved markedly. Blood counts remained essentially unchanged. The stiffness and pain in the knee disappeared. The patient could squat readily and for the first time in ten or fifteen years could put his left leg on his right knee. After dismissal, he rode horseback for a week without trouble. During the next week a twinge of pain affected the knee whenever he mounted his horse. This disappeared, and when he returned to the clinic a month later his knee was still symptom free. Old skin lesions had healed and new ones had not developed. Leukocytes were 88,000 and 72,000 and lymphocytes 84 and 91 per cent.

Significance cannot be attached to this result without further experience. Effects of cortisone and ACTH on leukemias and lymphomas will be reported by Drs. Stickney, Heck and Watkins.

CORTISONE AND ARTHRITIS OF CHRONIC ULCERATIVE COLITIS

Among 3 patients with chronic ulcerative colitis given cortisone or ACTH was 1 with complicating moderately severe subacute polyarthritis. Cortisone was given for thirty-six days. The arthritis disappeared; the remission has lasted over four months. Detailed results will be reported by Drs. W. H. Dearing and P. W. Brown.

ACTH IN GOUT AND GOUTY ARTHRITIS

Recently a close relation between gouty arthritis and adrenal cortex function has been demonstrated. Gouty patients excrete subnormal

41. Karlson, A. G.: Personal communication to the authors.

41a. Footnote 3*a*, *b* and *d*.

amounts of 17-ketosteroids according to various investigators,[42] who suggested that in gout biologic androgenic activity is maintained by a "gouty androgen" which, unlike other androgens, is metabolized without the significant production of 17-ketosteroids. ACTH given to patients with quiescent gout decreased serum urates and increased urate excretion according to Robinson, Conn, Block and Louis.[43] Three days after these investigators gave ACTH to 1 such patient a short attack of acute gouty arthritis developed. Thus these workers related the cyclic clinical and biochemical changes in gout to cyclic changes in adrenal activity and suggested that acute attacks of gouty arthritis occur during periods of decreased cortical function. Hellman [44] gave 150 mg. of ACTH daily for four days to 4 patients with quiescent gout. A few days later acute gouty arthritis developed in 2. When ACTH (200 mg. within thirty-eight hours) was given, the acute attacks promptly disappeared. Thus various factors which provoke acute gouty arthritis may do so in a common way, by affecting pituitary-adrenocortical activity.[45] Rapid amelioration in other cases of acute gouty arthritis by the use of ACTH, sometimes by a single injection of 50 mg., has since been reported.[46] Rebound relapses could be prevented by giving colchicine or salicylates or both immediately after discontinuing the use of ACTH.

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42. (*a*) Wolfson, W. Q.; Levine, R.; Guterman, H. S.; Hunt, H. D.; Cohn, C., and Rosenberg, E. F.: Endocrine Factors in Nucleoprotein Metabolism and in Gout, Ann. Rheumat. Dis. **7**:248 (Dec.) 1948. (*b*) Wolfson, W. Q.; Guterman, H. S.; Levine, R.; Cohn, C.; Hunt, H. D.; Rosenberg, E. F.; Kadota, K., and Turner, L.: An Endocrine Finding Apparently Characteristic of Gout: Very Low Urinary 17-Ketosteroid Excretion with Clinically Normal Androgenic Function, Arch. Int. Med. **9**:497 (June) 1949; abstracted, J. Clin. Endocrinol. **9**:497 (June) 1949. (*c*) Wolfson, W. Q.; Levine, R.; Cohn, C.; Hunt, H. D.; Guterman, H. S., and Rosenberg, E. F.: Adrenocortical Dysfunction in Gout, abstracted in Ann. Rheumat. Dis. **8**:311 (Dec.) 1949.

43. (*a*) Robinson, W. D.; Conn, J. W.; Block, W. D., and Louis, L. H.: Role of the Adrenal Cortex in Urate Metabolism and in Gout, Proc. Central Soc. Clin. Research **21**:23 (Oct.) 1948. (*b*) Robinson, W. D.; Conn, J. W.; Block, W. D.; Louis, L. H., and Katz, Joseph: Role of the Anterior Pituitary and Adrenal Cortex in Urate Metabolism and in Gout, Ann. Rheumat. Dis. **8**:313 (Dec.) 1949; J. Lab. & Clin. Med. **33**:1473, 1948.

44. Hellman, Leon: Production of Acute Gouty Arthritis by Adrenocorticotropin, Science **109**:280 (March 18) 1949.

45. Robinson and others.[43] Hellman.[44]

46. (*a*) Spies, and Stone.[37a] (*b*) Footnote 31*b* and *c*. (*c*) Robinson and others.[43a, b] (*d*) Margolis, H. M., and Caplan, P. S.: Treatment of Acute Gouty Arthritis With Pituitary Adrenocorticotropic Hormone (ACTH), J. A. M. A. **142**:256 (Jan. 28) 1950.

USE OF CORTISONE OR ACTH IN CERTAIN ALLERGIC AND OTHER NONRHEUMATIC CONDITIONS

Because certain nonrheumatic and allergic conditions, such as asthma, hay fever, egg sensitivity and migraine, are often relieved during jaundice or pregnancy, one of us stated his belief that when substance X was identified it might well be as useful in these conditions as in rheumatoid arthritis and fibrositis.[47] Neurodermatitis disappeared in 1 case (case 11), and symptoms of bronchiectasis were markedly reduced in another (case 3) during the use of cortisone. The hay fever of 2 of our rheumatoid patients (cases 10 and 22) gave little or no trouble during use of cortisone. Further investigations being carried out here, by Carryer and others, and elsewhere on the effect of cortisone or ACTH on these and other nonrheumatic conditions give promise that this hope may be fulfilled.[48]

OPTIMAL DOSAGE AND METHOD OF ADMINISTRATION OF CORTISONE OR ACTH

Further experience is needed to determine the optimal dosage and method of administration.

Dosage.—Because of the scarcity of material and the absence of previous experience to guide us, a rather empiric scheme of dosage was first used. When 50 or 75 mg. of cortisone proved inadequate, the daily dose was increased to previously effective doses of 100 mg. rather than to 85 or 90 mg. To determine the limits of tolerance and to obtain a prompt effect in patients with acute or severe conditions, such as rheumatic fever or lupus erythematosus, doses of 150 or 200 mg. were given for a few days on special occasions rather than, for instance, 125 mg. for many days. The same was at first true regarding the use of ACTH by ourselves and others. In the light of further experience it is apparent that doses were sometimes larger than necessary. But from these experiences valuable data have been gained, and something about the requirements and the limits of tolerance has been learned. It would appear that 100 mg. doses of ACTH compare roughly with 200 mg. of cortisone and that both these doses, if given daily, should be considered high, doses that are usually not well tolerated for long. A safer and usually as effective an initial daily dose would be 50 mg.

47. Footnotes 3*d*, 5*b* and 1*a*.

48. (*a*) Armour Conference on ACTH: Proceedings of the Conference on ACTH Sponsored by Armour & Co., Chicago, October 21 and 22, 1949, to be published. (*b*) Elkinton and others.[27k] (*c*) Carryer, H. M.; Koelsche, G. A.; Prickman, L. E.; Maytum, C. K.; Lake, C. F., and Williams, H. L.: The Effect of Cortisone upon Bronchial Asthma and Hay Fever Occurring in Ragweed-Sensitive Subjects, unpublished data.

of ACTH or 100 mg. of cortisone. Subsequent reduction of dosage with retention of full effect in rheumatoid arthritis seems to have been accomplished to date oftener with ACTH than with cortisone, at least in the hands of others. It has been determined that 50 mg. of cortisone daily may suppress mild rheumatoid arthritis, and it may be that daily doses of less than 100 mg. may be adequate in some severe cases. The tolerance of different patients for either hormone varies considerably.

Length of Administration.—Our early plan of more or less continued dosage developed, of course, from the fact that prompt relapses accompanied the withdrawal of the hormones; hence the early assumption that there might be an adrenal cortex deficiency rather than a tissue deficiency and that replacement therapy should be attempted. But soon that idea became untenable, and the indefinitely prolonged administration of either hormone appeared to be neither possible in most cases nor desirable. Although prudence and the desire to see whether the effects could be repeated governed the change to a plan of interrupted administration, certain clinical observations have suggested that such a plan may, in fact, be more physiologic.

Soon after an initial short relapse secondary partial symptomatic remissions, rebound eosinopenia, secondary decreases in sedimentation rates or secondary increases in urate excretion have occasionally been observed by us or others. Almost complete symptomatic remissions persisted for about two weeks after withdrawal of hormone in 3 of our cases (cases 6, 14 and 18), for one to three months in 3 more cases (cases 2, 13 and 22). A persistence of effect was even more striking in 3 other cases. In 2 cases (cases 5 and 7) the patients' remissions have continued for about ten and twelve months after withdrawal of the hormone. In the other case (case 11) articular relief lasted only four days after a first course (cortisone), two weeks or more after a second course (ACTH) and more or less completely for seven months after a third course (cortisone). Did the use of alternating courses of cortisone and ACTH have special merit in this case (although not in case 6)?

This suggests that sometimes the production or utilization of cortisone improved after use of the hormone was stopped. It suggests that more lasting effects, perhaps ones resembling natural spontaneous remissions, may be produced if we learn how to cooperate with, rather than attempt to dominate or supplant, the functions of the pituitary adrenal mechanism.

Prevention or Control of Side Effects.—In addition to the use of an interrupted or "course method" of administration for rheumatoid arthritis, other means of preventing or controlling undesirable side effects are under investigation. The intermittent use of estrone and progesterone during the second course of cortisone prevented most of

the annoying symptomatic side effects which one menopausal woman had during her first course on cortisone alone, and in another case testosterone decreased nitrogen deficit. Reduction of serum potassium has borne no constant relation to the symptom of weakness which developed in some patients after use of cortisone, but when a relationship appears to exist or if the concentration of serum potassium becomes significantly subnormal potassium chloride can be given orally. Rheumatic symptoms were often controlled by smaller doses than those required to reduce sedimentation rates to normal. It may be best to use the smallest dose which will control rheumatic symptoms adequately and not be concerned with sedimentation rates—in other words, to suppress or control symptoms, not rates.

Since the majority of our patients had no troublesome side effects while being given one of the hormones for periods varying from a few weeks to a few months, side effects will probably not present an important problem in the investigative management of most cases of acute rheumatic fever, acute gouty arthritis, acute crises of disseminated lupus erythematosus and other conditions, such as seasonal allergies or asthmatic crises, in which relatively short term administration may suffice.

Withdrawal of Hormone.—To prevent quick relapses, which, with rebound increases in sedimentation rates, may follow sudden withdrawal of either hormone, two methods of withdrawal have suggested themselves to us and to others: (1) to taper off the daily doses of cortisone or ACTH, giving successively smaller doses of either the last few days; (2) to conclude a course of cortisone with the use of ACTH for one or two days. In the first plan the adrenal cortex is, as it were, given warning that it will soon be "on its own." In the second plan the adrenal cortex function, depressed by the preceding use of exogenous cortisone, is aroused, stimulated to increased activity by a few doses of ACTH. But, having observed rebound relapses in only 2 of our 23 cases, we have usually purposely discontinued abruptly the use of either hormone, not only to determine the clinical and biochemical reactions to sudden withdrawal but to see whether the adrenal glands might be induced to adjust more quickly after successive courses, to respond more efficiently to sudden needs. Further experience will determine which plan is best.

SYNOPSIS AND CONCLUSIONS

The potential reversibility of rheumatoid arthritis has been further demonstrated.

Cortisone or the pituitary adrenal corticotropic hormone (ACTH) has been given to 23 patients with severe rheumatoid arthritis, to 8 patients (reported) with acute rheumatic fever, to 6 patients with severe

disseminated lupus erythematosus with or without associated polyarthritis, to 2 patients with tuberculous arthritis, to 1 patient with severe psoriasis and psoriatic arthritis, to 1 patient with primary osteoarthritis and to 1 patient with polyarthritis associated with chronic ulcerative colitis.

Cortisone, given to 21 patients with severe or moderately severe rheumatoid arthritis, produced a very marked effect in 12, a marked effect in 8 and a moderate effect in 1. Cortisone was administered, in some cases continuously, that is, daily for periods varying from eight to one hundred and eighty-seven days. It was given more or less continuously to 2 patients for a total of two hundred and fifteen and two hundred and eighteen days respectively. Daily doses varied from 25 to 300 mg. but were usually 100 mg. When patients received more than one course, they responded to each course in much the same manner.

The pituitary adrenal corticotropic hormone, ACTH, which stimulates responsive adrenal glands to make their own cortisone or a cortisone-like substance, such as compound F, was given daily to 6 patients with severe or moderately severe rheumatoid arthritis for periods varying from eleven to eighty-seven days. The antirheumatic effect was very marked in 4 cases and marked in 2 cases. The daily doses varied from 45 to 140 mg. but were usually 100 mg.

Most of the symptoms of rheumatoid arthritis responded promptly to cortisone or to ACTH in a characteristic pattern: reduction of stiffness first, then of pain on motion and then of tenderness and swelling. During the use of either hormone some patients became practically symptom free but others still had minor degrees of rheumatic activity: arthritis in miniature. The usual over-all relief was roughly about 80 to 90 per cent.

Miscellaneous clinical results from cortisone or ACTH included reduction of fever when present, improved nutrition with increased appetite and weight, frequent development of a sense of well-being or "euphoria," reduction or disappearance of several flexion contractures, and reduction in size of subcutaneous rheumatoid nodules and lymph nodes.

Sedimentation rates during the use of cortisone became normal in 15 cases, became almost normal in 3 and were reduced but not to normal in 3 cases. From ACTH, sedimentation rates became normal in all 6 cases. Rates of reduction were usually fairly rapid, occasionally tardy. Once reduced, the sedimentation rates in some cases remained normal as long as adequate doses of the hormones were given; in other cases they varied in the neighborhood of near normal values and in a few cases rose again.

Concentrations of hemoglobin and erythrocyte counts increased fairly rapidly in several cases. Abnormally increased serum globulin concentrations were reduced, and albumin-globulin ratios became more nearly normal.

A variety of metabolic and other biochemical effects were studied. In general they bore a quantitative relation to the doses of cortisone or ACTH used and to the duration of administration. There was a general tendency for an initial retention and later a liberation of salt and water and reduction of serum potassium, but in only 1 case was the last severe. Cortisone in doses of 100 mg. daily usually induced minimal or no alterations in plasma electrolytes or in balance for sodium, potassium, chlorides or nitrogen; but daily doses of 200 mg. of cortisone or of 100 mg. of ACTH sometimes produced a negative nitrogen balance and a transient hypochloremic hypopotassemic alkalosis. When present, the latter was often mild and apparently nonproductive of symptoms; occasionally it was marked and appeared to be correlative to certain symptomatic side effects.

No marked impairment of carbohydrate tolerance occurred among the 23 rheumatoid patients given cortisone or ACTH, although administration was prolonged in several cases. Fasting blood sugar levels remained normal: No significant glycosuria developed. Glucose tolerance tests were performed during the use of cortisone in 9 patients: Results were normal in 5 and abnormal in 4. It would appear that these hormones when given in the doses usually employed in our cases do not markedly reduce carbohydrate tolerance in rheumatoid patients who do not have latent or frank diabetes. But in any patient with latent or frank diabetes these hormones should be expected to produce transient reduction of carbohydrate tolerance.

Articular biopsies, made in several cases before and after receipt of various amounts of cortisone or ACTH, revealed that definite, sometimes marked, reduction of synovial and subsynovial inflammation resulted from use of the hormones.

When cortisone or ACTH was withdrawn, symptoms and signs of rheumatic activity usually returned, in most cases quickly. But in a few cases symptoms remained in abeyance for from two weeks to a few months, and in 2 cases the hormone-induced remissions have persisted for ten and twelve months respectively.

The prolonged use of either of these hormones may produce side effects of different types. Of the 23 rheumatoid patients no significant side effects developed among 9 (39 per cent): they received cortisone or ACTH for a total of about three weeks to four and one-half months. Mild side effects, such as mild acne, mild hirsutism, rounding of the face or mild irritability, developed among 8 patients (35 per cent) given continuously or almost continuously one of the hormones for from eleven

days to seven months. Moderate side effects developed in 2 patients (9 per cent) given cortisone or ACTH for a total of ninety-five and one hundred and one days. More disturbing or "marked" side effects developed in 4 patients (17 per cent) during the administration of cortisone or ACTH for from twelve to one hundred and eighty-seven days.

Most patients tolerated well 100 mg. of cortisone or a corresponding amount of ACTH daily for at least a month or two. When side effects occurred, they usually (but not always) developed in patients who received one or the other hormone continuously for a relatively long time or "large doses" for a shorter time. Although the development and nature of the side effects depended largely on dosage and duration of administration of the hormones, individual tolerances played a role. Males tolerated greater doses and longer administration than did females, especially adolescent or menopausal females.

A few side effects were related to current "impurities" in ACTH, not to ACTH itself. The hormonal side effects concerned shifts of fluid and electrolyte balance and characteristic changes in certain bodily tissues and functions. The commoner side effects consisted of certain transient paresthesias or somatic symptoms resembling those considered "functional" and may have resulted from transient vasomotor changes or transient alterations in tissue fluids and electrolytes. Other effects of hypercortisonism resembled those seen in Cushing's syndrome, such as rounded face (which occurred in 7 patients), amenorrhea (which occurred in 1 rheumatoid patient), mild hirsutism (which occurred in 7 patients), mild acne (which occurred in 2 patients) or striae (which developed in 1 patient). Minor alterations of psyche (euphoria, mild nervousness) often occurred. In 1 patient who received cortisone continuously for one hundred and eighty-seven days depression clearly developed after about five months and at one time became fairly severe.

A few side effects became evident not during but after the use of the hormones; chief of these withdrawal effects was a sense of exhaustion and weakness, which usually disappeared after four weeks or so. Temporary reduction of adrenal cortex function was considered as a possible cause.

These side effects have, to date, been transient and reversible.

No significant changes in blood pressure occurred in any of the rheumatoid patients. But in a patient with severe lupus erythematosus disseminatus with renal involvement, the blood pressure increased notably when the daily doses of cortisone were increased to 150 mg. Later, when the dosage was decreased, the blood pressure fell again.

The antirheumatic and certain other effects from ACTH were essentially the same as those from cortisone, but 100 mg. of ACTH apparently stimulates the production of considerably more than 100 mg. of cor-

tisone, perhaps 200 mg. or even more. Therefore, some of the effects, especially the side effects, from 100 mg. of ACTH were somewhat prompter and more marked than those from 100 mg. of cortisone. ACTH is, of course, effective only in patients with responsive adrenal glands. The adrenal glands of most, but not all, persons with rheumatoid arthritis are responsive. A patient with rheumatoid arthritis or another condition affected by these hormones will, if his adrenal glands are unresponsive, not benefit from ACTH but may respond to cortisone.

Compound A (11-dehydrocorticosterone) given to 3 patients had no effect on joints or on sedimentation rates.

Compound F (17-hydroxycorticosterone) decreased rheumatic symptoms and the sedimentation rate in 1 of our patients. This and other data suggest that cortisone and compound F have essentially the same antirheumatic activity, and in this paper no sharp line distinguishes one from the other. Compound F and not compound E (cortisone) was recovered from the urines of our patients given ACTH. This suggests that the human adrenal gland may deliver compound F in its secretion.

Acute manifestations of rheumatic fever were generally abolished promptly by cortisone or ACTH. No evidence of new, or increased old, rheumatic carditis was observed within the following eight to ten months. But it will take prolonged observation to evaluate the role of these hormones in the prevention or control of rheumatic carditis.

A patient with severe disseminated lupus erythematosus was markedly benefited by cortisone. Certain systemic manifestations regressed as well as associated arthritis.

A patient with severe psoriasis with psoriatic arthritis responded to cortisone and to ACTH.

Cortisone affected favorably certain hyperergic responses in 2 cases of tuberculous arthritis and reduced symptoms and sedimentation rates but did not produce bacteriologic or pathologic remissions.

An osteoarthritic joint of 1 patient became symptomless as a result of cortisone given for his leukemia. The articular and intestinal symptoms of chronic ulcerative colitis were notably affected by cortisone in 1 case. Without further experience, only limited significance can be attached to these isolated observations.

Coincidentally with the effect of cortisone on rheumatoid arthritis, symptoms of hay fever decreased in 2 cases and of bronchiectasis in 1 case; a chronic neurodermatitis cleared in 1. Further studies are being made by others to evaluate these observations.

The observations of others on the effects of cortisone and ACTH on certain articular conditions, especially gouty arthritis, were reviewed. Patients with mild rheumatoid arthritis responded to 50 mg. of cortisone daily.

Several articular and other inflammatory reactions have been temporarily relieved when adequate amounts of cortisone were provided. The action of cortisone appears to be group specific rather than disease specific or nonspecific. Perhaps cortisone constitutes one of the body's chief defenses against the action of certain agents on certain tissues.

Since in 74 per cent of our 23 rheumatoid patients no troublesome side effects developed while one of the hormones was being given for periods varying from two weeks to a few months, it would appear that side effects may not present an important problem in the investigative management of most cases of acute rheumatic fever, acute gouty arthritis, acute crises of disseminated lupus erythematosus and other conditions, such as seasonal allergies, in which relatively short term administration may suffice.

For those conditions which would seem now to require long-continued use, methods should be found to prevent, control or combat if possible undesirable side effects. So far, our attempts to do this have met with limited success: The combined use of estrone and cortisone appeared to prevent most of the annoying symptomatic side effects which developed in 1 menopausal patient from cortisone alone; nitrogen and potassium deficits, if they occur, can probably be controlled by special diets and the administration of potassium. Testosterone minimized the nitrogen deficit in 1 case. But the best guarantee against side effects now is to use, possibly intermittently, the smallest effective daily and total dose.

Daily doses of 200 mg. of cortisone or 100 mg. of ACTH should be considered "high," ones which may be well tolerated by most patients for fairly short periods only and from which side effects may usually be expected within a relatively short time. Such doses should be regarded as suitable only for short term use or for emergencies, such as acute crises of lupus erythematosus or acute rheumatic fever. Continued tolerance for daily doses of 100 mg. of cortisone or for comparable amounts of ACTH (50± mg.) is much greater. But whenever possible, or as soon as possible, the smallest effective doses should be used.

The optimal dosage and method of administration of cortisone and ACTH remain to be determined and may not be established without more information about the physiology and metabolism of ACTH, cortisone and compound F. A few data suggest that the intermittent administration of either hormone, or interrupted alternating courses thereof, may provide a more physiologic response than the use of either hormone given continuously to the limits of individual tolerance. In the presence of functioning adrenal glands, one must learn how to cooperate with them rather than to dominate them or to try to take over their functions.

As we have stated repeatedly, the use of these hormones should be considered an investigative procedure, not a treatment. The value of these hormones at present is that their use will permit the study of certain disease mechanisms more carefully than heretofore. We can now repeatedly produce controlled remissions of several diseases, to be followed by more or less controlled relapses, both of which processes can be studied intensively by a variety of clinical, biochemical and immunologic methods. It is hoped and believed that such studies will in time lead to an improved and practical method of treatment. But this present study is to be regarded, not as a report on clinical therapy, but as an investigation in clinical physiology.

RADIOACTIVE ISOTOPES IN THE STUDY OF PERIPHERAL VASCULAR DISEASE

III. Further Studies on the Circulation Index with an Evaluation of the Diagnostic and Therapeutic Value of Priscoline®

MORRIS T. FRIEDELL, M.D.
WALTER INDECK, M.D.
AND
FENTON SCHAFFNER, M.D.
CHICAGO

THE CONDITION of the peripheral vascular circulation can be estimated by means of radioactive isotopes. A method in which radioactive phosphorus is used to test the status of the peripheral circulation has been described.[1] Data so obtained not only afford a survey of circulatory efficiency but can be helpful as a guide to prognosis and treatment. The method is applicable to the investigation of new drugs designed to treat peripheral vascular disease. This report is concerned with some observations on the use of 2-benzylimidazoline hydrochloride (priscoline®),[2] whose effect occurs chiefly at the termination of the sympathetic nerves in the vascular smooth muscle. It may also have a direct histamine-like effect on the smaller vessels.[3] According to Wirsa and Ottoman,[4] the action of the drug is complex, causing peripheral vasodilatation and increased cardiac output.

CIRCULATORY INDEX AS DETERMINED BY RADIOISOTOPES

Two hundred microcuries of radioactive phosphorus (P^{32}) as a phosphate ion is injected intravenously, and a thin-walled beta counter is applied to the sole.

From the Hektoen Institute for Medical Research of the Cook County Hospital and the Peripheral Vascular Clinic, Mercy Hospital.

1. (*a*) Friedell, M. T.; Schaffner, F.; Pickett, W. J., and Hummon, I. F.: Radioactive Isotopes in the Study of Peripheral Vascular Disease: I. Derivation of a Circulatory Index, Arch. Int. Med. **83**:608-620 (June) 1949. (*b*) Schaffner, F.; Friedell, M. T.; Pickett, W. J., and Hummon, I. F.: Radioactive Isotopes in the Study of Peripheral Vascular Disease: II. Method of Evaluation of Various Forms of Treatment, ibid. **83**:620-632 (June) 1949.

2. The priscoline® was furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

3. Grimson, K. S.; Reardon, M. J.; Marzoni, F. A., and Hendrix, J. P.: The Effects of Priscol on Peripheral Vascular Diseases, Hypertension, and Circulation in Patients, Ann. Surg. **127**:968-990, 1948.

4. Wirsa, T., and Ottoman, R.: Influence of Benzyl-Imidazoline on the Peripheral Circulation of Man, Proc. Soc. Exper. Biol. & Med. **70**:647-650, 1949.

The counts per minute, determined with a scaling unit, are plotted semilogarithmically with time as the logarithmic function. The values ordinarily fall in a straight line; the reciprocal of the slope of this line is designated the circulatory index.

The equation for this index can be expressed as

$$CI = \frac{\text{Log } 20 - \text{Log } 2}{TCTs_{20} - TCTs_2} = \frac{1}{TCTs_{20} - TCTs_2},$$

where CI is the circulatory index, $TCTs_{20}$ the theoretic number of counts at twenty minutes and $TCTs_2$ the theoretic number of counts at two minutes.

The index can be altered by subjecting the patient to treatment directed at producing vasodilatation. Peripheral vasodilators such as histidine and ascorbic acid, tetraethylammonium chloride, lumbar blocks and sympathectomy have been investigated previously and their effects on the circulatory index determined.[1b] The most useful part of the study of peripheral vascular circulation with isotopes is the alteration of the circulatory index by means of one of these vasodilators. Priscoline® was added to this series in an effort to find a safe, rapidly acting vasodilator as a diagnostic aid in the type of study we are undertaking.

The circulatory index of normal persons is usually above 0.110, and averages 0.160. When the index falls below 0.110, it is felt that it is in the arteriosclerotic range (the average for the arteriosclerotic group is 0.089). The theoretic basis for this difference has been discussed elsewhere.[1] Within a few minutes after injection of the isotope, the average arteriosclerotic patient will accumulate more of it in the tissues of his extremities than will a person with normal circulation. This apparently paradoxic difference is attributed to peripheral capillary dilatation in the arteriosclerotic limb. The dilated capillary, it is postulated, permits a more rapid interchange of the isotope with the stable ions in the tissue fluids.[1a] The capillary dilatation in arteriosclerosis is, it is felt, due to chronic anoxia. On this basis, alteration of the circulatory index by means of peripheral vasodilators is indicative of the response of the capillary bed. The relationships of these alterations in index to prognosis on a clinical basis have been discussed,[1b] but further evaluation with use of priscoline® has been made. Determination of the circulatory index was not limited to patients with arteriosclerosis obliterans but was also extended to patients with other abnormal peripheral vascular conditions. To date, our experience with use of the index for patients with proved Buerger's disease is still too meager to permit any statistical comparison. We do not deem the method useful in other diseases. As will be emphasized in a separate report, the value of the method lies primarily in the selection of those patients most likely to respond favorably to lumbar sympathectomy.

SIGNIFICANCE OF GROUPINGS

Four main types of responses of the circulatory index have been noted. In group I the circulatory index is initially in the arteriosclerotic range and rises to normal after therapy. In group II the index is low and falls to a lower level after treatment. The index in group III seems to be subject to variation. Therefore, we now divide this group into two subgroups: (*a*) the patients in whom the initial index is above 0.110 and falls into the arteriosclerotic range after treatment and (*b*) the patients in whom the initial index is above 0.110, but below the mean of the normal group, and rises beyond the normal range after treatment. In group IV the index is above the normal range and rises even higher after treatment.

Classifications by groups to date have been correlated with clinical findings in 82 instances. Patients expressing subjective and objective manifestations of relief from a single dose of the drug, for example, were

TABLE 1.—*Clinical Results Correlated with Type of Alteration of Circulatory Index (Group) Following Treatment with Peripheral Vasodilators*

Group	Number of Cases	Number of Good Results	Percentage of Good Results
I	20	19	95
II	16	15	93.75
III *a*	25	19	76
III *b*	11	5	45.5
IV	4	0	0
Ungrouped	6	2	33.33

classified as having a good result even though the therapy was not continued. Thus a patient responding well to an injection of priscoline® or a paravertebral lumbar block might subsequently be submitted to sympathectomy or to a prolonged oral treatment with priscoline® and the results further evaluated by both clinical tests and redetermination of the circulatory index. Results with any form of therapy were usually consistent even though interchanged, with the exception of several lumbar blocks which could be classified as technically incomplete or failures. The correlation of clinical (subjective and objective) results with the type of alteration obtained in the circulatory index (grouping) is shown in table 1. Patients in groups I and II yield the best clinical responses. Patients in group III *a* do better than do those in group III *b*; treatment was ineffective for the few patients in group IV. It was not possible to determine a grouping in 6 instances, because there was no apparent alteration in the index following therapy. These failures could be attributed to a number of factors: insufficient medication, inaccurate lumbar block and inability of the vascular system to respond to inhibition of sympathetic fibers. Inherent mechanical and electronic

lags in the counting apparatus will occasionally cause failures. We have found that good curves are not obtainable if the radioactivity which is measured yields counts of the order of 3,000 per minute or higher. Therefore, it is wise to allow a lapse of a week or more between tests to permit reduction in residual radioactivity. There is no apparent harm from the tracer doses used, but it is better not to administer P^{32} too frequently to any patient. The few patients who gave erratic or nonclassifiable curves, however, responded poorly from a clinical basis. It is likely that the vascular systems of these persons were not responsive to medication or interruption of the sympathetic chain.

CHOICE OF METHOD FOR ALTERATION OF CIRCULATORY INDEX AND DETERMINATION OF GROUP

Since determination of the group is of considerable importance, a readily available vasodilator is preferred. Lumbar block, while not difficult, is not suitable for an outpatient clinic. It is much more effective when performed by an experienced operator, and it is best reserved for conditions in which causalgic features predominate. Tetraethylammonium chloride is quite effective but produces a marked fall in blood pressure. It is satisfactory especially in those cases with predominant causalgic features.

TABLE 2.—*Clinical Results Correlated with Type of Alteration of Circulatory Index (Group) Following Treatment with Priscoline®*

Group	Number of Cases	Number of Cases with Prompt Clinical Improvement
I	11	11
II	3	3
III *a*	3	2
III *b*	3	1
No change in index	2	1

Changes in the circulatory index occur with priscoline® as with any other sympatholytic agent. Twenty patients showed an alteration in circulatory index following an intravenous dose of priscoline.® In 2 additional patients no change in the index was accomplished. Table 2 illustrates the distribution and results by groupings. These cases were predominantly in group I, and in these the results were good. The 2 patients who showed no response to intravenous injections of priscoline® were given 300 mg. daily of the medication orally. One had symptomatic relief with healing of a chronic ulcer of the foot, but the other continued to complain bitterly of pain in the foot and intermittent claudication. In table 3 are shown the results in 10 patients who were

treated with orally administered priscoline® for long periods. Patients in group I improved when treated with oral doses of priscoline® except those who complained of severe pain. These persons probably would have responded better to direct interruption of the sympathetic nerve supply to the affected area. We have found that priscoline® must be given to the limit of tolerance, and the dosage may be increased gradually (about 300 mg. a day is the maximum that we have used). Unpleasant side effects may interfere with treatment, as will be brought out later.

The following case illustrates a favorable type of response to priscoline.®

C. M., a 76 year old white man, was admitted to the Cook County Hospital on Feb. 8, 1948. He complained of a painful left foot for the past month. The pain

TABLE 3.—*Illustrations of Typical Effects of Orally Administered Priscoline in Various Disorders, Together with Groupings as Determined by Change in Circulatory Index*

Group	Diagnosis	Result
I	Arteriosclerotic ulcer	Ulcer healed with 200 mg. of priscoline® a day
I	Causalgia	No relief of pain
I	Buerger's disease	Complete relief of claudication with 200 mg. of priscoline® a day
I	Raynaud's disease (trophic change of hands)	Moderate relief, although disease was far advanced
III *a*	Arteriosclerosis diabetes	Relief of symptoms with 200 mg. of priscoline® a day
III *a*	Popliteal embolism	Amputation necessary because of progressing gangrene in spite of use of priscoline® and sympathectomy
III *b*	Severe causalgic state	No relief of pain
Ungrouped	Auricular fibrillation; popliteal embolism; severe cardiac failure	No relief with 200 mg. of priscoline® a day; patient obtained relief from block of lumbar portion of sympathetic chain with absolute alcohol; extremity preserved

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was so severe that any motion of the foot during sleep would awaken him. There was a history of diabetes for twenty-five years, and the patient was well regulated on a diet and 25 units of protamine zinc insulin daily. The blood pressure was 158 mm. of mercury systolic and 100 mm. diastolic. Both lower extremities showed pyoderma in the healed and crusted stages. The right leg was normal except for the skin lesions and absence of peripheral pulsations. The toes of the left foot were cold and cyanotic. There was a reddened edematous area measuring 7 cm. in diameter on the medial aspect of the dorsal surface of the left foot. The preliminary circulatory index was 0.130 (chart 1). The patient was treated with sedatives and opiates, and conservative treatment was directed to the involved foot. On Feb. 15, 1949, the patient returned for further study. There was neither subjective nor objective change in his status. He was given 75 mg. of priscoline® intravenously and experienced immediate relief. The index was now 0.90 (chart 1). This change was consistent with group III *a*. One hundred and fifty milligrams of priscoline® was given orally in divided doses daily. A few days following the institution of the therapy, the use of opiates was discontinued. After four weeks of

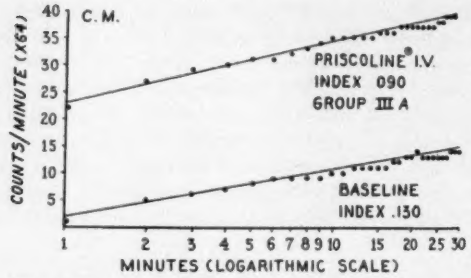

Chart 1.—The lower curve illustrates the circulatory index prior to treatment. The upper curve illustrates the circulatory index after an intravenous dose of priscoline.®

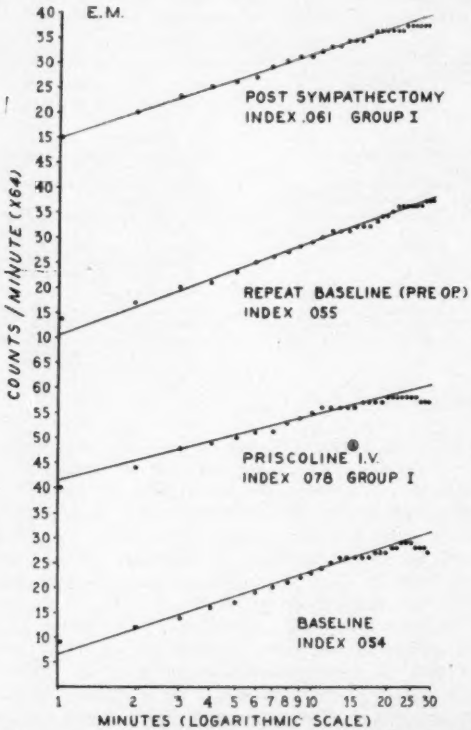

Chart 2.—Sequence of curves illustrating circulatory index before and after treatment with intravenous injection of priscoline® (lower two), and before and after sympathectomy (upper two). Note that the base line curves are identical although taken at different times. Note also that priscoline® and sympathectomy similarly affect the curve illustrating the circulatory index.

oral therapy, the redness and cellulitis on the dorsal aspect of the foot subsided and the toes became warm and pink. The patient was discharged completely free from pain and objectively improved.

The case just described is one in which a satisfactory therapeutic regimen was maintained. Undesirable side effects, including dizziness, bizarre headaches and gastrointestinal complaints, occasionally interfere with therapy. Such a problem was presented in the next case.

E. M., a 41 year old white man, was first seen by us on Feb. 11, 1949. At this time he complained of weakness of the feet, with slight pain in the instep of one year's duration; cramps in the calves after walking one block, and coldness and pain in the right foot for the past five months. The patient also stated that the superficial veins of the leg would temporarily become tender and painful. Thrombosed veins were palpable in both legs, and arterial pulsations were absent below the knees. A diagnosis of Buerger's disease was made. The initial index was 0.054 (chart 2). One week later, after an injection of 75 mg. of priscoline® intravenously, he experienced a feeling of warmth and tingling sensations in both lower extremities. At this time his index changed to 0.078 (chart 2), which is consistent with group I. The patient was given 75 mg. of priscoline® orally per day and the dosage was increased gradually to 150 mg. per day before any beneficial effects were noticed. Relief was maintained for a period of six weeks. At this time the patient complained of headaches, postprandial distress and chilly sensations. It was necessary to decrease the dosage to 100 mg. daily before the undesirable effects disappeared. This dosage failed to relieve his symptoms, and the medication was discontinued. On May 3, 1949, the patient's index had fallen approximately to the original base line (0.055) (chart 2). The right lumbar sympathetic chain was interrupted on May 8, and the postoperative course was uneventful. On June 6, the last determination was made and the final index was 0.061 (chart 2). Warmth of the right leg was experienced after the operation. There was no claudication in the right leg after the operation, and the patient had a marked decrease in the amount of thrombophlebitis. The subjective difference was so great that the patient requested sympathectomy on the opposite side, which was performed with good results.

SUMMARY

The use of a radioactive isotope (P^{32}) in determining the status of the peripheral arterial circulation is further considered. The reciprocal rate of deposition as plotted on a semilogarithmic curve has been designated as the circulatory index. The change in the index produced by vasodilatation can be used as a guide to selected therapy. From this change in the circulatory index, patients have been placed in one of four categories. Prognosis has been shown to be consistently more favorable in group I and poorer in the subsequent groupings. Group III has been divided into two subgroups. It is possible that group III *b* can be classed with group IV. In the latter groups we are reluctant to advise sympathectomy, since treatment of any type is useless.

Intravenous injections of priscoline® have been used in recent months to determine these groupings. In addition, oral medication with this drug over prolonged periods has been employed for therapy of various

peripheral vascular disorders. We have found its use safe and only occasionally interfered with by unpleasant side reactions. It is apparently more effective in those conditions in which the symptoms are due primarily to diminished blood supply. When there is a superimposed severe causalgic state, relief is not always obtained. Direct interruption at the level of the sympathetic ganglions seems to be more effective in these conditions. The importance of selecting patients who will respond favorably to sympathectomy is obvious. (A later report will reveal that the method has proved useful in eliminating instances of precipitous gangrene following sympathectomy, as reported by Freeman [5] and others.)

P^{32} in the quantity necessary to perform these tests is apparently harmless, and the value of the tests to the patient is great. The technic is simple and requires little elaborate equipment. Failures have occurred because of technical errors, especially if the residual radioactivity is allowed to interfere with the sensitivity of the counter. We have found that coincident counting is a source of error when the counting rate exceeds 3,000 counts per minute. At present, we are attempting to standardize the method with smaller doses of P^{32}. One hundred microcuries of radioactive phosphorus gives a fairly smooth curve and permits completion of the determination of grouping in one day.

CONCLUSIONS

1. Priscoline® (2-benzylimidazoline hydrochloride) when administered intravenously will alter the circulatory index as determined with radioactive-phosphorus.

2. The prognosis of the groups as determined with priscoline® coincides with that of groups determined by other vasodilating mechanisms.

3. Priscoline® is apparently more effective in conditions primarily due to interference with the blood supply. It is less effective in severe associated causalgic states.

4. Orally administered priscoline® is useful in the management of certain disorders of the peripheral vascular system.

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SUBACUTE BACTERIAL ENDOCARDITIS

Follow-Up Study of Thirty Patients Treated with Penicillin

PHILIP L. PILLSBURY, M.D.
SAN FRANCISCO
AND
MARSHALL J. FIESE, M.D.
FRESNO, CALIF.

IT IS NOW five years since patients with subacute bacterial endocarditis were first successfully treated with penicillin. From the first it was apparent that good immediate results could be expected in a great majority. Enough time has now elapsed to permit a preliminary appraisal of the end results of penicillin treatment. Recent studies have shown increasing interest in this aspect of the disease. Many observers, particularly Fiese [1] and, later, Rapoport and Ellis,[2] have commented on the appearance of cardiac insufficiency. This complication, rather than inadequate antibiotic therapy, has generally been recognized as the most frequent source of failure. Other studies, however, emphasize embolic phenomena, aneurysms and renal failure as well. Christie,[3] in his study of 269 patients treated with penicillin, listed 73 deaths due to either heart failure alone or heart failure in combination with other causes. There were 8 deaths from uremia, 15 from embolic effects, 10 from hemorrhage and 25 from mixed or uncertain causes. Jones and others [4] reported a series of 33 penicillin-treated patients with 15 deaths, 5 of which were from cardiac failure alone, 3 from grossly elevated blood urea levels and the remainder from a combination of these causes and embolic episodes; in other reported series of penicillin-treated patients, deaths from uremia, embolism and hemorrhage have occurred about as frequently.[5] Occasional instances of either late relapse or reinfection have

From the Department of Medicine, Stanford University School of Medicine.

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5. (*a*) Paul, O.; Bland, E. F., and White, P. D.: Experiences with Penicillin Therapy at the Massachusetts General Hospital, 1944-1946, New England J. Med. **237**:349, 1947. (*b*) Priest, W. S.; Smith, J. M., and McGee, C. J.: Penicillin Therapy of Subacute Bacterial Endocarditis, Arch. Int. Med. **79**:333 (March) 1947.

TABLE 1.—*Follow-Up Status of 31 Treated Patients with Bacterial Endocarditis*

Patient	Age, Years	Sex	Heart Lesion	Observation Time, Months: Before Treatment	During Treatment	After Treatment	Nature of Follow-Up	Condition of Patient	Previous Reports
1	22	M	Coaretation of aorta	3	1½	47	Hospital entry	Hard at work doing physical labor; no symptoms	Case 1 [9a]
2	42	F	Mitral stenosis	2½	2	3	Autopsy	Died of heart failure	Case 2 [9a]
3	34	M	Mitral stenosis	5	2	9	Letter *	Committed suicide after months of progressive heart failure	Case 3 [9a]
4	20	M	Aortic stenosis and insufficiency	½	2	46	Letter *	Has sedentary occupation; no symptoms	Case 4 [9a]
5	58	M	Mitral insufficiency (?)	2	2	44	Outpatient study	At work without symptoms	Case 5 [9a]
6	64	M	Mitral insufficiency	2	2	47	Telephone	Feeling perfectly well, doing heavy labor; refused to enter hospital for study	Case 7 [9a]
7	59	F	Mitral stenosis	2	2	48	Hospital entry; no autopsy	Died of carcinoma of breast; considerable exertional dyspnea without gross cardiac failure	Case 6 [9a]
8	65	F	Mitral stenosis	1½	2	15	No autopsy	Died after cerebrovascular accident, probably not embolic	Case 9 [9a]
9	18	F	Aortic stenosis and insufficiency	5	2	43	Hospital entry	Had 2 subsequent pregnancies without cardiac difficulty; no symptoms	Case 8 [9a]
10	24	M	Aortic insufficiency and mitral stenosis	3	⅛	..	Autopsy	Died of blockade of right coronary orifice by a large vegetation	Case 11 [9a]
11	29	M	Aortic insufficiency	1	2	11	Autopsy *	Died of heart failure at another hospital	Case 10 [9a]
12	22	F	Undiagnosed	2	2	42	Letter	Doing housework; no symptoms; 1 subsequent pregnancy without cardiac difficulties	Case 2 [9b]
13	23	M	Aortic insufficiency and mitral stenosis	5	2	44	Hospital entry	Had borderline cardiac reserve, hemiparesis with moderate return of function	....
14	60	M	Aortic insufficiency	1	3	..	No autopsy	Had recurrence 14 days after first course; died of cardiac failure during second course of treatment	Case 3 [9b]
15	32	M	Aortic insufficiency and mitral stenosis	1½	2	45	Hospital entry	Had no cardiac symptoms, hemiparesis with moderate return of function	....
16	47	M	Aortic and mitral stenosis and insufficiency	½	2	37	Hospital entry	Had exertional dyspnea, hemiplegia with nearly complete return of function	Case 5 [9b]
17	30	F	Aortic insufficiency	2½	2	43	Hospital entry	Doing housework and athletics; no symptoms	....
18	27	M	Aortic stenosis and insufficiency, mitral stenosis	¾	2	35	Coroner's report	Died of sudden heart failure during active exercise; had several episodes of tachycardia, no other cardiac symptoms	Case 6 [9b]

TABLE 1.—*Follow-Up Status of 31 Treated Patients with Bacterial Endocarditis—Continued*

Patient	Age, Years	Sex	Heart Lesion	Observation Time, Months: Before Treatment	During Treatment	After Treatment	Nature of Follow-Up	Condition of Patient	Previous Reports
19	32	M	Aortic stenosis and insufficiency	2	3	35	Hospital entry	Working as cabinet maker; no symptoms	Case 1 [9b]
20	24	M	Aortic insufficiency	1	2	37	Hospital entry	Doing moderately restricted activity; no symptoms	....
21	42	F	Mitral stenosis	2	7½	34	Hospital entry	Pneumonia developed 21 months after treatment completed, with uneventful recovery; no symptoms	Case 1 [9c]
22	68	M	Aortic insufficiency	5	2	2	Autopsy *	Died of progressive cardiac failure, hemorrhage into interventricular septum with mural thrombus	....
23	54	M	Aortic insufficiency	1(?)	2	34	No autopsy	Died after 28 months of progressive heart failure	....
24	66	M	Aortic stenosis (calcific?)	4 ..	5½ 1	31 ..	Hospital entry	Had recurrence after 31 months; cardiac failure twice after strenuous activity; transferred to another hospital, infection uncontrolled	Case 24 [9c]
25	39	M	Aortic stenosis	5	16	25	Outpatient study	Had several courses of treatment before infection controlled; no symptoms	Case 3 [9c]
26	18	F	Congenital heart lesion complicated by rheumatic carditis 6 years previously	2 2	2 2	24 5½	Hospital entry Outpatient study	Had recurrence after 24 months Apical diastolic murmur developed after second infection; no symptoms	....
27	39	M	Undiagnosed	1	6	21	Letter *	Had hematuria, possibly from acute pyelonephritis studied elsewhere; no cardiac symptoms	Case 4 [9c]
28	43	M	Mitral insufficiency	½	6	18	Telephone	Hard at work as a plumber; refused to enter hospital for study	Case 5 [9c]
29	45	M	Undiagnosed	2	4	20	Hospital entry	Had no symptoms other than anxiety neurosis	Case 7 [9c]
30	41	M	Aortic insufficiency and mitral stenosis	6(?)	5	..	Autopsy	Died of cardiac failure with infection uncontrolled; mycotic aneurysm and ruptured aortic leaflet noted at autopsy	Case 6 [9c]
31	43	M	Aortic stenosis	3	2	27	Hospital entry	Had convulsive seizures following cerebral embolus, hemiparesis with moderate recovery; no cardiac symptoms	....

* Data forwarded by patient's local physician.

been reported.[6] Studies concerning the conditions of valvular architecture and immunity necessary for bacterial implantation have predicted a special liability to reinfection for patients convalescing from bacterial endocarditis.[7] Clinical evaluation of this liability has been clouded, however, by the finding of deeply embedded bacteria in the valves of successfully treated patients at autopsy.[8]

MATERIAL

Experiences with the first 31 patients with proved diagnoses of bacterial endocarditis to be treated with penicillin at Stanford Hospital form the basis of this report. These patients were admitted for treatment in the years 1944 to 1946. Clinical details and particulars of treatment in many of these cases have been reported previously.[9] There were 23 male and 8 female patients. Patient 10 died after only four days of treatment; the data in this case were not further considered in the present study. The other patients were followed either until death or until the year 1948. Of the remaining survivors, 13 entered the hospital for this study, 1 was observed in the outpatient department, 3 replied by letter and 2 replied by telephone. Ten patients died. Frequent visits to outpatients and occasional hospital entries provided data for the intervening period. Observations included, when possible, a history of the interval, physical examination, blood count, determinations of the sedimentation rate, the serum urea or creatinine level, the Addis count, the venous pressure and the circulation time, the making of an electrocardiogram and of roentgenograms of the chest at 7 feet (213 cm.) and whatever further study seemed indicated in the individual case.

RESULTS

A summary of the follow-up status of these 31 patients is presented in table 1. Of the 10 deaths, 8 were due to heart failure and 2 to unrelated causes, occurring a sufficient length of time after treatment to convince us that the effects of the infection on the hearts had become

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6. (*a*) Christie.[3] (*b*) Jones and others.[4] (*c*) Paul, Bland and White.[5] (*d*) Cannady, E. W.: The Successful Use of Penicillin in the Treatment of Subacute Bacterial Endocarditis, Illinois M. J. **93**:94, 1948. (*e*) Thill, C. J., and Meyer, O. O.: Experience with Penicillin and Dicumarol in Treatment of Subacute Bacterial Endocarditis, Am. J. M. Sc. **213**:300, 1947. (*f*) Rosenberg, M. J.: Subacute Bacterial Endocarditis: Report of a Case of Reinfection, J. A. M. A. **138**: 956 (Nov. 27) 1948.

7. Keefer, C. S.: The Pathogenesis of Bacterial Endocarditis, Am. Heart J. **19**:352, 1940.

8. Carnes, W. H., and Tinsley, C. M.: The Pathologic Results in Cases of Bacterial Endocarditis Treated with Penicillin, Stanford M. Bull. **4**:78, 1946.

9. (*a*) Bloomfield, A. L.; Armstrong, C. D., and Kirby, W. M.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. Clin. Investigation **24**:251, 1945. (*b*) Bloomfield, A. L., and Halpern, R. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis: Some Problems, J. A. M. A. **129**:1135 (Dec. 22) 1945. (*c*) Clark, W. H.; Bryner, S., and Rantz, L. A.: Penicillin-Resistant Non-Hemolytic Streptococcal Subacute Bacterial Endocarditis, Am. J. Med. **4**:671, 1948.

static. The general mortality was 33 per cent. The mortality is given by age in table 2 and by survival time in table 3. In computing the latter, data for survivors who failed to qualify for the period under consideration were discarded.

To provide a clinical classification of the results of treatment, we divided our patients into the following categories:

Patients Not Cured.—In this category we included patients 14 and 30. Both died of heart failure before treatment was completed, so they do not represent failures of treatment in the strict sense Nonetheless they died while the infection was active, and from that viewpoint they represent failures.

TABLE 2.—*Mortality According to Age*

Condition of Patient	Age, Years				
	15 to 24	25 to 34	35 to 44	45 to 54	Over 55
Surviving	7	3	5	2	3
Died of heart failure	0	3*	2	1	2
Died of unrelated cause	0	0	0	0	2†

* Including patients 3 and 18.
† Patients 7 and 8.

TABLE 3.—*Length of Survival After Start of Penicillin Treatment*

Condition of Patient	Months				
	2 to 4	5 to 9	10 to 18	19 to 36	37 to 50
Surviving	28	25	22	21	14
Died of heart failure	2	5	7	8	9
Died of other causes	0	0	1	1	2

Patients Cured but in Whom Cardiac Insufficiency Developed.—In this category we included 6 patients (2, 3, 11, 22, 23 and 24). Of these, only patient 24 was still alive at the end of the period of study. The borderline which demarcates cardiac insufficiency from cardiac disease with adequate compensation in the presence of valvular deformity is indistinct. Four other patients (7, 13, 16 and 25) exhibited varying degrees of limitation of activity. They could be included here. In particular, patient 16 experienced mild heart failure, evidenced by congestive rales, hepatic engorgement, venous pressure of 14.5 cm. and circulation time of 22 seconds, one month after treatment was finished. However, with rest and regulation with digitalis he responded well. At the end of the observation period, all 4 patients in the latter group were compensated. Patient 18 provided a rather unusual instance of cardiac failure: Repeated bouts of tachycardia developed after treatment. One of these was proved to be supraventricular by a fortuitous electro-

cardiogram. Sudden death occurred during a period of apparently excellent health, while the patient was on a skiing trip. The coroner's report indicated cardiac insufficiency (possibly from a disturbance of mechanism).

Patients Apparently Cured but in Whom Relapse or Reinfection Occurred Later.—There were 2 patients in this category. The details follow:

Case 1 (patient 24).—A 68 year old Negro entered the hospital Aug. 28, 1945, because of fever and weakness of four months' duration. He had known of a "leaky valve" for the past six years but denied having had rheumatic fever. He had received injections for five weeks at another hospital for treatment of the fever. Physical examination revealed that he was obviously sick. There was a petechia in the left conjunctiva. The blood pressure was 100 systolic and 60 diastolic. The heart was thought to be enlarged. There was an apical systolic thrill and a loud, rough, holosystolic apical murmur. The spleen was not felt. Roentgenograms revealed a cardiac silhouette interpreted as at the "upper limits of normal" in size. Later studies showed calcium deposits in the area of the aortic valve and demonstrated bilateral renal calculi. A nonhemolytic streptococcus sensitive to 0.2 units of penicillin per cubic centimeter was isolated from the blood stream. Treatment with 22,250,000 units of penicillin over sixty days produced a satisfactory clinical and bacteriologic response. Subsequent cultures were sterile until Nov. 12, 1946, when frank cardiac failure brought the patient to the hospital. He responded well to digitalis and remained symptom free on restricted activity. On Aug. 3, 1948, failure again developed after three months of considerable physical activity. He was then found to have obstructive uropathy. Resection of the prostate gland was carried out on August 20. The day before the operation a prophylactic dose of 50,000 units of penicillin was given intramuscularly every three hours; this was continued until the twentieth postoperative day. Therapy was then changed to the administration of aqueous procaine penicillin, 600,000 units daily. Cultures of blood taken on September 15, 16, 17 and 21 all grew a nonhemolytic enterococcus requiring 4 to 8 units of penicillin per cubic centimeter for inhibition. Urine cultured simultaneously grew a nonhemolytic enterococcus of different cultural characteristics. A five day trial with aureomycin, 4 Gm. daily, was ineffective. The patient was then given aqueous procaine penicillin, 9,600,000 units daily, for twenty-eight days; with this dose, serum penicillin levels of 40 to 66 units per cubic centimeter were maintained. The clinical response was satisfactory, although relapse occurred a few days after the patient was transferred to another hospital for convalescent care.

Case 2 (patient 26).—A young woman of 18 years, studied at this hospital twelve years previously for the interesting combination of active rheumatic fever and a congenital heart lesion, was admitted Feb. 1, 1946, after two months of fever associated with pains in the right hip and knee. Physical examination at that time revealed that she was severely ill. The blood pressure was 105 systolic and 55 diastolic. The heart was not enlarged, the rhythm was regular and there was a loud apical systolic murmur. Diastole was clear. There was no clubbing of the fingers and no cyanosis, and the spleen was not felt. A nonhemolytic streptococcus sensitive to 0.1 unit of penicillin per cubic centimeter was isolated from the blood stream. The patient was treated with 100,000 units of amorphous penicillin every six hours for twenty-two days. Observation of a blood culture positive for nonhemolytic streptococcus then prompted a change to 50,000 units

every three hours. After a total of 24,100,000 units had been given over a period of sixty days, treatment was stopped and the patient discharged from the hospital. After treatment, repeated blood cultures were sterile. The temperature, pulse, white cell count and sedimentation rate remained normal until the first week of February 1948, when fever and arthralgia returned. The patient was readmitted on March 29. Physical examination showed no changes other than the appearance of an apical systolic thrill. A nonhemolytic streptococcus sensitive to 0.1 unit of penicillin per cubic centimeter was again isolated from the blood stream. Cultural characteristics, so far as could be determined, were identical with those of the organism first isolated. Treatment consisted of the administration of 600,000 units of crystalline procaine penicillin G in oil, twice a day for fifty days, with a satisfactory clinical and bacteriologic response. Since treatment an apical diastolic murmur has developed, but the patient is otherwise well at the time of this report.

Patients Cured in Whom Cardiac Compensation Was Maintained but Some Other Complication Occurred. — Patients with Emboli: Embolic phenomena were commonly observed after completion of an effective period of treatment. Petechiae of the skin and conjunctivas,

TABLE 4.—*Embolic Phenomena Occurring After Start of Adequate Therapy*

	Interval, Months			
	1 to 2	3 to 6	6 to 12	Over 12
Cerebral embolus	0	1	0	0
Pulmonary embolus	3	0	0	1
Petechiae, subungual hemorrhage or Osler's node	6	4	1	1
Other *	1	2	0	0

* Embolism of palmar arch, retinal artery or mesenteric artery (1 each).

splinter hemorrhages of the nail beds, and Osler's nodes were classified as minor episodes and emboli of larger arteries as major episodes. Minor episodes were observed in 13 patients at least one month after the start of treatment. In patient 1 subungual hemorrhages were observed twenty-six months after treatment. Major episodes occurred in 8 patients at least one month after treatment was started. Cerebral emboli occurred in patient 16 three months prior to the start of therapy; in patient 15, at the start, and in patients 31 and 13, respectively, two weeks after and three months after therapy. All the patients are living at the time of writing, with varying degrees of return of function. Mortality among patients exhibiting major and minor episodes was not significantly different from that of the group as a whole. The details are presented in table 4.

Patients with nephritis: At the start of therapy, abnormalities of the urine were frequent and characteristic of the disease. After therapy, however, few patients exhibited abnormalities, either of the urine or of renal function. Patients 8 and 24 were excluded from this classification because of bilateral bifid pelvis and bilateral renal calculus,

respectively. Of the remaining only 5 (patients 1, 12, 23, 25 and 31) demonstrated even the slightest proteinuria after treatment, and among these the urinary sediment was unimpressive. In no patient in this series was the serum creatinine or serum urea level significantly elevated at the end of the follow-up period. Addis count studies of the urine were possible for 8 patients. These findings are presented in table 5.

Patients with Disease not Related to Bacterial Endocarditis.—Patients 7 and 8 died of disease not related to bacterial endocarditis. These deaths had no bearing on the effectiveness of penicillin treatment but necessarily terminated the follow-up period. Fortunately, both

TABLE 5.—*Renal Studies of 13 Patients at Close of Observation Period*

Patient	Period Observed, Months	Specific Gravity *	*pu* *	Protein, Gm.*	Casts, Millions Per 24 Hr.*	Red Cells, Millions Per 24 Hr.*	White and Epithelial Cells, Millions Per 24 Hr.*	Blood Urea, Mg./ 100 Cc.	Serum Creatinine, Mg./ 100 Cc.
1	47	1.016	5.5	0.09	0	0	0	..	1.5
7	47	.....	...	....	..	..	..	30	...
9	43	1.026	5.8	0.07	0.01	0	0.6	34	1.2
13	42	1.020	6.0	0	0.05	1	4	44	0.7
15	40	.....	...	....	..	..	..	..	0.9
16	37	1.015	6.0	0.06	0	0.01	1.5	45	...
17	43	.....	...	....	..	..	..	..	0.7
19	35	1.026	6.0	0	0.3	0	0	43	1.3
20	37	1.024	5.8	0.18	0	1	39	..	...
23	31	.....	Alkaline	2.3	..	..	..	28	0.9
26	27	1.010	6.0	0	0.2	2	1	..	0.76
29	20	1.020	6.0	0.01	0.08	0.5	3	..	1.25
31	20	.....	Alkaline	0.46	No formed elements in acid specimen			..	1.2

* Timed specimens collected overnight and calculated in terms of a 24 hour period according to the method of Addis (Glomerular Nephritis: Its Diagnosis and Treatment, New York, The Macmillan Company, 1948, pp. 10-19).

patients survived long enough to convince us that the infection was cured and that its effect on the heart was complete.

Patients Cured in Whom Cardiac Compensation Was Maintained and No Other Complications Occurred.—In this category there were 13 patients (1, 4, 5, 6, 9, 12, 17, 19, 20, 21, 27, 28 and 29) in whom therapy was an unqualified success. Many are engaged at the time of this report in occupations requiring strenuous physical exertion; none are significantly handicapped in their daily lives.

The clinical appearance of these patients generally correlated well with the laboratory observations. Values for circulation time and venous pressure were always normal in the absence of obvious cardiac decompensation. With the completion of penicillin therapy, the sedimentation rate returned to normal except in patient 2 and remained so. The

white cell count, temperature and hemoglobin concentration returned to normal when the bacteremia was controlled. On the other hand, changes in the transverse cardiac diameter and in the electrocardiogram continued for an unexpectedly long period after the infection was controlled. To be certain that these changes were real, the electrocardiograms were all reviewed and the transverse cardiac diameters remeasured. In computing the latter, malpositioning of the patient and the general configuration of the cardiac silhouette were taken into account; questionable films were disregarded.

Transverse Cardiac Diameter: Measurements were taken from serial roentgenograms made at a distance of 7 feet during therapy and at frequent intervals in the follow-up period. Increases in transverse cardiac diameter amounting to less than 1 cm. were disregarded, those amounting to more than 1 cm. but less than 2 cm. were classified as "slight" and those amounting to more than 2 cm. were classified as "significant." It so happened that the diameter of no heart enlarged by more than 2 cm. failed to exceed one-half the endothoracic diameter. Among those surviving the observation period (and patients 7 and 8) with initially normal-sized hearts, 4 showed no enlargement, 8 "slight" enlargement, and 5 "significant" enlargement without gross signs of failure. For 1 patient of this group there were insufficient data. Three hearts were initially enlarged. Among these, 1 showed a further significant increase, 1 showed no change and 1 had decreased significantly in size. If the hearts of patients who survived for a period of six months or more after treatment are included, there were a total of 16 initially normal-sized hearts enlarged to some degree. Of these, 6 enlarged mainly during treatment and 10 mainly after treatment. Among the entire group the interval from the completion of successful therapy to the taking of the earliest roentgenograms to demonstrate a transverse cardiac diameter within 1 cm. of the maximum was 9.6 months. The range was four to twenty-two months. In none of this group was there any diminution of size, once acquired. Among the group of hearts enlarging during treatment 1 returned to pretreatment size.

Electrocardiographic Studies: Atrial fibrillation, flutter or both occurred at some time in 4 patients. In 1 other patient atrial fibrillation was constantly present. Atrioventricular conduction time was prolonged to greater than 0.20 seconds in 7 patients. In 4 of these the P-R interval was prolonged, with a subsequent decrease to normal values. In 5 additional patients the P-R interval increased to the upper limit of normal, but in 2 of these the increase was associated with the administration of digitalis glucosides. In 2 other patients the P-R interval was initially at the upper limit of normal and remained so. In 14 patients the P-R interval was normal throughout. Of these 4 died

within six months of treatment, and in 1 the observations were limited. Thus, disturbances of atrioventricular conduction occurred in roughly 50 per cent of our patients. The configuration of QRS complexes and T waves was completely normal for 6 patients. Minor changes in T wave pattern not associated with the administration of digitalis glucosides, consisting of flattened or diphasic T waves in leads II and III and minor elevations or depressions of the RS-T interval in limb and precordial leads, were encountered in 14 patients. More definite T wave changes were found in 3 patients. Four patients had Q waves in lead III of significant depth and usually of transient appearance. QRS

TABLE 6.—*Duration of Heart Changes After Completion of Treatment*

Patient	Heart Lesion	Transverse Diameter *	P-R Interval	T Wave Change	Observation Period
1	Coarctation of aorta	4†	½	11	47
3	Mitral stenosis	7	..	..	9
4	Aortic stenosis and insufficiency	6	.	..	46
5	Mitral insufficiency (?)	..‡	—	..	20
6	Mitral insufficiency	19	..	..	19
7	Mitral stenosis	7	42	..	48
9	Aortic stenosis and insufficiency	—§	..	..	43
12	Undiagnosed	10	..	3	22
15	Aortic insufficiency and mitral stenosis	13	25	25	45
18	Aortic stenosis and insufficiency, mitral stenosis	—	—	—	18
19	Aortic stenosis	..	—	34	35
20	Aortic insufficiency	9	9	..	37
21	Mitral stenosis	22	..	..	34
24	Aortic stenosis	9	21	..	31
25	Aortic stenosis	—	—	..	25
28	Mitral insufficiency	—	—	—	4
29	Undiagnosed	—	..	..	20
31	Aortic stenosis	—	—	—	20

* Earliest point at which the transverse diameter approached within 1 cm. of the maximum transverse diameter observed.
† All figures indicate months after completion of treatment.
‡ Indicates no changes observed at all.
§ — indicates changes confined to period of treatment.

complexes of durations of 0.11 seconds or greater and of transient appearance were observed in 3 patients. One patient presented the appearance of left bundle branch block (this patient was not included among those showing T wave changes). In none of the patients was a pattern of myocardial infarction found, and in none was the evolution compatible. As a matter of fact, the evolution of these changes described no characteristic pattern at all. Abnormalities appeared and disappeared without correlation with the patient's general course. Particularly was this so in patient 18. However, in 7 patients these changes came to an end abruptly enough to fix the time of their occurrence. The temporal

relationships of change in transverse cardiac diameter, change in P-R interval and changes in T wave configuration correlated with the heart lesion are shown for 18 patients in table 6. In the remaining 12 patients there either were no changes or the data were inadequate. When— appears in the table, the changes occurred during the period of treatment. None of these late changes was reflected by an increase in the sedimentation rate or the white cell count, or by elevation of the temperature.

COMMENT

Excluding those who died of unrelated causes, the mortality in our series of patients was 29 per cent. The principal cause of death of each patient was heart failure. Fiese [1] analyzed all these deaths save those of patients 18, 23 and 30, all of whom died after his paper was written. The factors which he outlined as predisposing to heart failure remain valid. Briefly, these factors are age, duration of infection before treatment, preexisting cardiac failure, severity of illness and after-treatment. In our experience there was no relation between the dose of penicillin and survival, provided the infection was controlled. Failure of the first course of penicillin did not contribute to a worse prognosis after a second or third try. Christie,[8] however, recorded a significant increase in mortality when retreatment was necessary.

More difficult to assess was the effect of the infection on the prognosis of the underlying heart disease. For this purpose even five years is not a very long period of observation. In those cases, however, in which there were adequate laboratory data, the period was sufficient to indicate that changes may continue for a year or more after the completion of successful treatment. These data were not of the sort which determined whether such changes result solely from damage of a mechanical nature to the heart muscle and valves, or whether they are also a slowly developing response of hypersensitive nature. A review of the anatomic findings among those patients who were examined at autopsy at this hospital demonstrated little evidence of an allergic response. Mild proliferative glomerulitis was encountered frequently, but in no case were lesions of active rheumatic fever described.

Death of 2 of our patients was clearly due to gross mechanical disturbances, in 1 from a block at the orifice of the right coronary artery and in the second from perforation of an aortic cusp. Accidents of this sort are widely encountered and require no further comment. However, valvular deformity of insidious progression may develop from the cicatrix of the cured lesion. Changes in the character of the heart sounds and murmurs are common in active bacterial endocarditis. Some change was encountered during the convalescent stage in 5 of our patients (4, 21, 25, 26 and 31). In the last 4 this change concerned the

appearance of a diastolic murmur where none had been heard before. It is logical to suppose that valvular distortion also occurs generally when bacterial inflammation is engrafted on a valve in those patients in whom no change in the character of murmurs is detected. The problem is to determine the importance of these valvular changes relative to the development of heart failure.

The association of rheumatic carditis and bacterial endocarditis is well known. Numerous authors [10] have described localized infiltrations of round cells, collagen necrosis, and multinucleated giant cells closely resembling in structure typical Aschoff nodules, distributed throughout the myocardium in patients with bacterial endocarditis. Pappenheimer and von Glahn [11] described proliferating endocardial verrucae typical of those of rheumatic endocarditis. MacIlwaine [12] correlated the age of the Aschoff nodules with the duration of bacterial infection in 11 of 17 patients with bacterial endocarditis due to a variety of organisms. Leaving aside the entirely theoretic aspects of pathogenesis which these studies raise, the practical aspect of this association is important in the convalescent care of the patient.

What are the clinical evidences of this association? With the infection active it is difficult to separate the suppurative from the nonsuppurative complications of bacterial endocarditis. With the infection controlled, however, the nonsuppurative complications are easily studied. Our own experience indicates that they are not severe. The changes found are restricted, with respect to the heart, to increases in the transverse cardiac diameter, increases in atrioventricular conduction and T wave changes. Of these, the T wave changes are the least striking and the most difficult to analyze. They are nonspecific in nature and undergo no characteristic evolution. The correlation of changes in transverse cardiac diameter and in atrioventricular conduction is presented in table 7 for those patients surviving long enough and for whom there was sufficient study to make the data reliable. For the purpose of this comparison, prolongation of the P-R interval to 0.20 second is

10. Saphir, O., and Wile, S. A.: Rheumatic Manifestations in Subacute Bacterial Endocarditis, Am. Heart J. **9**:29, 1933. Buchbinder, W. C., and Saphir, O.: Heart Failure in Subacute Bacterial Endocarditis, Arch. Int. Med. **64**:336 (Aug.) 1939. Clawson, B. J., and Bell, E. T.: A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, ibid. **37**:66 (Jan.) 1926. Gross, L., and Fried, B. H.: The Role Played by Rheumatic Fever in the Inflammation of Bacterial Endocarditis, Am. J. Path. **13**:769, 1939.

11. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **55**:173 (Feb.) 1935.

12. MacIlwaine, Y.: The Relationship Between Rheumatic Carditis and Subacute Bacterial Endocarditis, J. Path. & Bact. **59**:557, 1947.

classified as "slight" and prolongation to more than 0.20 second as "significant." One patient exhibited a prolongation of the P-R interval from 0.12 to 0.18 second in spite of tachycardia with a rate of 136 beats per minute. This patient was classified as exhibiting "slight" prolongation. The series was too small for more elaborate analysis, but the connection between these two measurements at least suggests a diffuse myocardial defect rather than valvular distortion. The data did not provide a basis to differentiate a rheumatic process from a widespread focal embolic myocarditis. The duration of effects may favor the former, but the total lack of continuing evidences of inflammation (in sedimentation rate, white cell count or temperature values) in any of our patients did not encourage this diagnosis.

Major embolic phenomena occurring late in the course of treatment or following it have been not infrequently encountered by others [13] as well as by us. Cerebral hemorrhage has also been described; this complication did not occur in our series. These episodes were not associated with the recurrence of infection. After the friable vegetations have healed, there is no special relation of embolic effects distinct from that which occurs with other conditions of the heart. The case of patient 22 provided a pathologic basis on which to base our conclusions. We assumed that late emboli proceed from mural or atrial thrombi. However, unlike thromboembolic disease from other causes, the prophylactic exhibition of anticoagulants is probably not justified in view of the frequent occurrence of cerebral hemorrhage complicating this therapy.[14]

Of the 13 patients who continued to have minor embolic episodes (Osler's nodes, petechiae, subungual hemorrhages) one month or more after the start of adequate therapy, 8 survived long enough and were subjected to sufficient study for data on them to be included in table 7. Six of these had significant cardiac enlargement with initially normal-sized hearts, and 2 had slight enlargement. Moreover, 1 patient showed prolongation of the P-R interval from a normal value to more than 0.2 second, 3 showed prolongation to this limit and 4 showed no prolongation. Whatever the nature of these minor episodes, embolic or allergic, their association with continuing cardiac changes was curious.

The complete absence of continuing renal lesions in this series was surprising. Glomerular nephritis is a reasonably common complication of bacterial endocarditis. It is described as particularly common in "bacteria-free" patients.[15] Christie [3] reported uremic deaths in 8 of his

13. Christie.[3] Jones and others.[4] Paul, Bland and White.[5a] Priest, Smith and McGee.[5b]

14. Duff, I. F., and Shull, W. H.: Fatal Hemorrhage in Dicumarol® Poisoning, with Report of Necropsy, J. A. M. A. **139**:762 (March 19) 1949.

15. Keefer, C. S.: Subacute Bacterial Endocarditis: Active Cases Without Bacteremia, Ann. Int. Med. **11**:714, 1937.

269 patients. Of these, 3 occurred during treatment and 5 after treatment was completed. Jones and his co-workers [4] described 3 patients who died with grossly elevated blood urea levels. They stated that uremia in these patients was an important but not the only contributing cause of death. Others have reported single cases of glomerular nephritis. A higher incidence of renal lesions was indicated in pathologic studies. Christian [16] showed that of 61 patients with active bacterial endocarditis there were focal embolic lesions in the kidneys of 91.8 per cent and diffuse glomerular lesions in those of 80.3 per cent. McLeod and Finney [17] were able to produce experimental lesions indistinguishable from those of glomerular nephritis in 19 of 57 animals by injecting killed cultures of alpha hemolytic streptococcus into the

TABLE 7.—*Correlation of Change in Transverse Cardiac Diameter with Change in Atrioventricular Conduction Time*

	Conduction Time					
	Initially Normal			Prolonged with Decrease to Normal	Upper Limit of Normal Throughout	Atrial Fibrillation or Flutter
Transverse Cardiac Diameter	No Change	Slight Increase	Significant Increase			
Initially normal						
No change	3	1	0	0	0	0
Slight increase	3	1	3	0	1	0
Significant increase	3	4	0	0	1	2
Initially enlarged						
Decrease	0	0	0	1	0	0
No change	0	0	0	1	0	0
Increase	0	0	0	0	0	1

renal artery. The relation of these pathologic and experimental data to our clinical results is difficult to explain. A study of frequently collected timed urine specimens demonstrated a rapid return to normal, generally occurring a few days after control of the bacteremia and always by the time treatment was completed, with the exceptions of patient 23 (who had severe heart failure) and 2 others who had preexisting renal defects.

We have described 2 cases of either late relapse or recurrence of infection. Of these, case 2 (patient 26) strongly suggests relapse. The organisms responsible for the infections were identical in cultural characteristics and in sensitivity to penicillin. This circumstance is in accord

16. Christian, H. A.: The Kidneys in Subacute Streptococcus Viridans Endocarditis, J. Mt. Sinai Hosp. **8**:427, 1942.

17. McLeod, N., and Finney, G. G.: Acute Experimental Glomerulitis Following Injection of Streptococcus Viridans into the Renal Artery, Bull. Johns Hopkins Hosp. **51**:300, 1932.

with the report of Carnes and Tinsley,[8] which indicates that bacteria may be found deep in the valves of apparently cured patients. Case 1 (patient 24), on the other hand, was certainly one of reinfection. The circumstances of this reinfection, which occurred in spite of intensive prophylactic penicillin therapy, illustrate the special liability to infection of patients with healed bacterial endocarditis. Rosenberg [6f] stated the belief that the recurrence in his case, which occurred two years after successful therapy, was an instance of reinfection in view of the demonstration of an apical abscess from which he cultured the causative organism. Three of Christie's patients [3] and 1 in the series reported by Paul, Bland and White [6a] showed late recurrence of infection. No differentiation of relapse and reinfection was made in either study. Thill and Meyer [6e] reported a recurrence one year after successful treatment, following extraction of a tooth and in spite of prophylactic administration of penicillin. Cannady [6d] reported a recurrence eleven months after successful penicillin treatment, also following extraction of a tooth. As the time span between treatment and recurrence increases, the probability of reinfection is greater than that of relapse. However, at present there seems to be no reasonable time limit which may be set to differentiate between these two mechanisms.

Prophylactic administration of penicillin is a widely accepted technic for the prevention of reinfection. We have used it in all our patients undergoing oral surgery or other operative manipulations. It is important to point out, however, that the basis for such penicillin prophylaxis is not entirely sound. Thill and Meyer [6e] and we encountered reinfection in spite of prophylactic administration of penicillin; unfortunately, a relatively resistant organism was to blame in both patients. The moral of these experiences is that very large doses of penicillin or combined penicillin and streptomycin should be used particularly when the likely source of entry is the genitourinary tract or the lower part of the bowel.

SUMMARY

This study concerns 31 patients with bacterial endocarditis treated with penicillin at Stanford Hospital in the years 1944 to 1946. Of these, 1 died after only four days of treatment. The remainder were followed either until death or until the year 1948. This represents an average follow-up period of thirty-five months for the surviving group.

1. During the period of study 10 patients died, 8 of heart failure and 2 of unrelated causes. One patient was still alive, but with overt heart failure and a recurrence of the infection still uncontrolled at the close of the period. Of those surviving, all but 8 showed clearcut evidence of cardiac damage, determined with electrocardiograms, by roentgenographic measurement of heart size or in both ways.

2. Two patients experienced late recurrence of the infection twenty-four and thirty-one months, respectively, after successful treatment. One of these instances may represent relapse, the other reinfection.

3. Major embolic phenomena occurred in 8 patients at least one month after the start of adequate therapy. Petechiae, subungual hemorrhages and Osler's nodes appeared variously in 13 patients more than one month after therapy was started. Embolic episodes are without significance as to the effectiveness of antibacterial therapy.

4. None of the patients showed evidence of a continuing renal lesion.

PROLONGED VASOCONSTRICTION DUE TO ERGOTAMINE TARTRATE

Report of a Case with Recovery, with Objective Evaluation of Vascular Findings

WALTER S. THOMPSON Jr., M.D.

WILLIAM W. McCLURE, M.D.

CHICAGO

AND

MILTON LANDOWNE, M.D.

Associate Chief, Section of Gerontology and Cardiovascular Diseases, Baltimore City Hospital

BALTIMORE

ERGOT poisoning following therapeutic administration of ergotamine tartrate may manifest itself as a vasoconstrictive response which may progress to gangrene. There is apparently an increased sensitivity of the vessels to the vasoconstrictive action of this derivative of ergot in hepatic disease, exophthalmic goiter, acute infections (particularly puerperal sepsis) and preexisting vascular disease.[1]

The pathogenesis of the vascular lesions with subsequent necrosis in experimentally induced ergotism was studied in the fowl's comb by Lewis and Gelfand.[2] They concluded that ischemia of the vessel wall with resulting endothelial change and stasis was a prerequisite for thrombosis and necrosis. Inasmuch as they found that a similar sequence of events followed mechanical interference with the circulation, they stated that direct poisoning of the tissues seemed to play no part. Vascular changes in man progressing to gangrene following the therapeutic use of preparation of ergot have been described.[1] The histopathologic factors appear to be the same as in the experimental animal. The evidence accumulated suggests that vasoconstriction alone, without secondary intimal change, does not lead to stasis, thrombosis and tissue necrosis.

Recently a patient came under observation presenting a history of vasoconstrictive phenomena of severe degree and long duration, which

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From the Department of Medicine, University of Chicago.

This study was aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago and the Lilienthal Fund for Research on Hypertension of the University of Chicago.

1. Yater, W. M., and Cahill, J. A.: Bilateral Gangrene of Feet Due to Ergotamine Tartrate Used for Pruritus of Jaundice: Report of Case Studied Arteriographically and Pathologically, J. A. M. A. **106**:1625 (May 9) 1936.

2. Lewis, T., and Gelfand, B.: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning, Clin. Sc. **2**:43, 1935.

were due to repeated self injection with ergotamine tartrate [3] and which did not progress to gangrene. On withdrawal of the drug and institution of therapy there remained no clinical evidence of arterial insufficiency in the previously involved areas. This status was substantiated by biopsies of muscle, plethysmographic studies and determinations of skin temperature.

The purpose in reporting this case is threefold: first, to present further evidence suggesting that in ergotism tissue necrosis does not develop in the presence of prolonged vasoconstriction without organic vascular change; second, to point out that in this patient, despite prolonged vasoconstriction, normal physiologic response of the involved vessels was retained, and, third, to suggest the place of sodium nicotinate as an effective vasodilating agent in the therapy of patients in this vasoconstrictive state.

REPORT OF CASE

Mrs. H. G., a white housewife aged 47, entered the clinic with a five month history of pain in the calves and thighs after walking short distances. Beginning as painful cramps in the left calf, the disease gradually progressed to involve both calves and both thighs. At the time the patient was first seen, walking only one half block would regularly produce pain that necessitated rest for relief. For three months she had noticed coldness of the lower portions of both legs and of both feet.

For twenty years the patient had been subject to "migraine" headaches, and for the past eight years she had been administering ergotamine tartrate to herself every time she had a headache, obtaining relief on each occasion. For the first several years she took 0.25 to 0.5 mg. of ergotamine tartrate intramuscularly two or three times a week. For the past two years she had taken the same dose almost daily, and occasionally twice a day.

The past history included poliomyelitis at the age of 9 years with residual atrophy of the left leg and the left thenar eminence. The gait was only slightly impaired. At age 24 symptoms of peptic ulcer developed; a duodenal crater was demonstrated roentgenographically. Thereafter she had recurrent exacerbations of the ulcer symptoms, but they always responded well to medical management.

Physical examination on admission showed a well developed, slender white woman in no evident distress. Contributory findings were confined to the extremities. The left thenar eminence was atrophic, as were all muscle groups of the left calf. Pulsations of both radial arteries were palpable. Pulsations in the posterior tibial and dorsalis pedis arteries were not palpable in either lower extremity. Below an abrupt line of demarcation the distal two thirds of each leg, including the foot, was cold and moderately cyanotic. There was no evidence of tissue necrosis.

Examination of the urine was noncontributory. A routine blood count revealed 9,900 white blood cells per cubic millimeter, 10.5 Gm. of hemoglobin per hundred cubic centimeters and 3,100,000 red blood cells per cubic millimeter.

A diagnosis of arterial insufficiency secondary to prolonged administration of ergotamine tartrate was made, and administration of the drug was discontinued. On the second day of hospitalization examination of the lower extremities showed

3. The preparation used was gynergen,® a product of Sandoz Chemical Works, Inc., New York.

no change. In the afternoon of that day the patient complained of a severe headache and was given 140 mg. of sodium nicotinate intravenously. A generalized flush accompanied the injection and was closely followed by a marked change in the physical findings in the extremities. The level of temperature change became less distinct, and the pulsations in the dorsalis pedis and posterior tibial arteries became palpable bilaterally. On subsequent examination there was no subjective or objective evidence of arterial insufficiency. The feet were warm, pulsations were good and walking distances previously productive of pain caused no distress. It was at this time that the studies to be described were made.

The improvement was not transient. The patient was followed for two months, remaining completely free of intermittent claudication and having no further headaches.

METHODS OF STUDY

Biopsies of muscle were made for the purpose of histologic study of the blood vessels, a specimen being obtained from a previously involved area of each calf. Determinations of blood flow in the lower portion of the right leg and in the right foot were made with a plethysmograph after venous occlusion, according to a method previously described.[4]

Observations were made for twenty minutes for control purposes with the patient at rest in the recumbent position; for twenty minutes following the subcutaneous injection of ergotamine tartrate, 0.5 mg.; for forty minutes following the intravenous injection of a similar amount of the same drug; for forty minutes following the intravenous injection of priscoline® (2-benzyl-4, 5-imidazoline hydrochloride),[5] 10 mg., and for five minutes following the intravenous injection of sodium nicotinate, 70 mg. During the control period blood flow was determined following circulatory arrest of three minutes' duration. The flow determined immediately on release from arterial occlusion (at the onset of reactive hyperemia) is designated as "hyperemic" flow.

The blood pressure in the right arm was determined at frequent intervals throughout the study period with a mercury sphygmomometer, using the recommended technic. Skin temperatures were obtained by means of a McKesson dermalor® after exposure to room temperature. These values were determined before and one hour after spinal anesthesia. Procaine hydrochloride, 100 mg., was injected intrathecally to produce an anesthetic level to the tenth and eleventh thoracic interspaces. The blood pressure before and for a period of one hour after anesthesia remained essentially unchanged at 116 systolic and 68 diastolic.

RESULTS

Microscopic examination[6] of the muscular material removed from the left leg for biopsy revealed fat, fibrous tissue and shrunken muscular remnants. There was some thickening of the arteries, but this was minimal and of the degree anticipated to accompany the muscular changes. These findings were interpreted as being a residual of the old poliomyelitis. In the sections from the muscles of the right calf the vessels were normal. Aside from a questionable prominence of the sarcolemma nuclei, the muscle fibers revealed no change.

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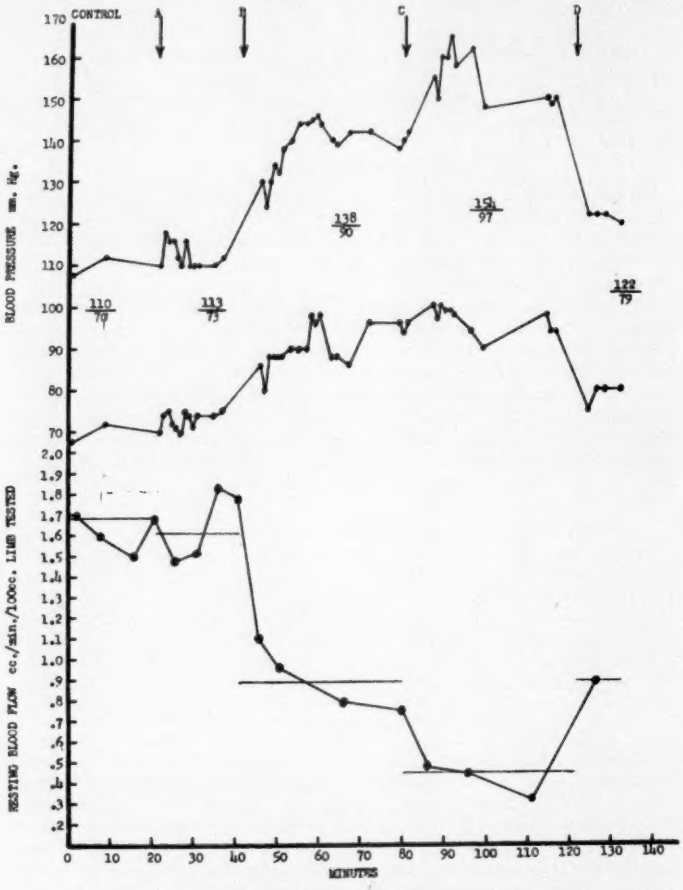
4. Landowne, M., and Katz, L. N.: A Critique of the Plethysmographic Method of Measuring Blood Flow in the Extremities of Man, Am. Heart J. **23**:644, 1942.

5. The drug was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

6. Dr. Eleanor M. Humphreys made the histologic interpretation.

Data concerning the blood flow in the lower portion of the right leg and in the right foot (volume, 1,560 cc.) and the blood pressure in the right arm are presented in the chart. During the control period the flow averaged 1.67 cc. per minute per hundred cubic centimeters of limb tested. This is within the normal



Blood pressure (right arm recumbent) and resting blood flow in the right leg and foot of the patient during the control period and after the administration of the following: *A*, 0.5 mg. ergotamine tartrate subcutaneously; *B*, 0.5 mg. ergotamine tartrate intravenously; *C*, 10 mg. priscoline® intravenously and, *D*, 70 mg. sodium nicotinate intravenously. Figures represent average systolic and diastolic pressures for each period. Values for blood flow represent averages of two to fifteen determinations each. Horizontal lines represent average blood flow for each period.

range (0.76 to 6.56 cc. per minute) as determined by our method. Average pressure was 110 systolic and 70 diastolic. The blood flow immediately following release from circulatory arrest of three minutes' duration (during reactive hyperemia) was determined during the control period and found to be 12 cc. per minute per hundred cubic centimeters of limb tested. This is well within the normal range of "hyperemic flow" as tested by our method.

After subcutaneous injection of 0.5 mg. of ergotamine tartrate there was no subjective sensation. During the subsequent twenty minute period there was a slight decrease in the average blood flow and a slight increase in the average systolic and diastolic pressure. Neither change was believed to be significant. On the intravenous injection of 0.5 mg. of ergotamine tartrate there was a prompt drop in the blood flow. This persisted, and during the next forty minutes the flow gradually decreased to a minimum of 0.75 cc. per minute per hundred cubic centimeters of limb tested. The average blood flow for this period was 0.89 cc. per minute. There was an accompanying pressor response which increased average pressures from 113 systolic and 73 diastolic to 138 systolic and 90 diastolic. Subjectively there were sensations of pounding in the head, occipital headache and

Skin Temperatures Before and One Hour After Low Spinal Anesthesia*

Site	Before		After		Increase	
	R	L	R	L	R	L
Lower portion of thigh	31.0	32.2	33.0	33.3	2.0	1.1
Midportion of calf	32.1	32.3	34.0	34.7	1.9	2.4
Ankle	31.8	32.8	33.7	34.1	1.9	1.3
Heel	31.4	32.2	34.0	34.4	2.6	2.2
Dorsum of foot	31.7	32.2	34.4	32.3	3.0	0.1
Midplantar region of foot	32.0	30.7	34.9	34.6	2.9	3.9
Great toe	29.4	30.8	35.0	34.4	5.6	3.6

* Centigrade.

nausea. These symptoms began three minutes after the injection and lasted throughout the entire period.

Forty minutes after the injection of ergotamine tartrate intravenously, 10 mg. of priscoline® was given by the same route. During the next forty minute period there was continued decrease in the blood flow, the minimum being 0.32 cc. per minute per hundred cubic centimeters of limb tested. The average for the period decreased to 0.45 cc. per minute per hundred cubic centimeters of limb tested. The pressor response further elevated the blood pressure to an average of 154 systolic and 97 diastolic. Subjectively there was little change, though the patient stated that her "head felt better."

At the end of this period, when the decrease in the blood flow and the elevation of the blood pressure were maximal, 70 mg. of sodium nicotinate was injected intravenously. There was a prompt increase in the blood flow to an average of 0.95 cc. per minute per hundred cubic centimeters of limb tested. An accompanying fall in the blood pressure was noted, the average pressure being 122 systolic and 79 diastolic. Before the injection (requiring about one minute) was completed a generalized flush became apparent and the patient "felt warm all over except below the knees."

Values for skin temperature before and one hour after low spinal anesthesia are indicated in the table. The greatest increase in temperature was noted in the distal portion of the leg and in the feet and toes.

COMMENT

Despite the history of a prolonged period of vasoconstriction and the definite objective signs of arterial insufficiency at the initial examination, there was no evidence of tissue necrosis. The vessels examined in the biopsy sections revealed no organic change attributable to the prolonged administration of ergotamine tartrate. These findings tend to support the previous evidence that vasoconstriction alone, without secondary intimal change, does not produce gangrene in ergotism. It may well be argued that the vessels examined were not sufficiently near the periphery, and that others more distal might have revealed such organic change. In this study such a possibility cannot be excluded, but the vessels observed were well within the involved area.

The subcutaneous injection of 0.5 mg. of ergotamine tartrate did not induce vasoconstriction during the twenty minute period of observation, as measured either by elevation of the blood pressure or by decrease in the peripheral blood flow. It has been demonstrated [7] that after the subcutaneous administration of 0.5 mg. of ergotamine tartrate 4 of 6 normal control patients exhibited a significant decrease in peripheral blood flow within twenty minutes. In this study there was no reason to suspect delayed absorption. Although ergotamine tartrate produces inconstant and complex changes in the peripheral circulation of the normally innervated limb,[8] the failure to provoke a demonstrable vasoconstrictive response in this patient suggests that an increased sensitivity to the drug had not developed and that the initial clinical findings were due to a cumulative effect of the drug.

The ability of the previously involved segment of the arterial system to dilate was retained. This was demonstrated by the increase in blood flow following release from arterial occlusion (reactive hyperemia) and by the increase in skin temperature following spinal anesthesia.

After the administration of priscoline® there was accentuation of the pressor effect, chiefly in the systolic component, and a further increase in peripheral vasoconstriction, as measured by a further decrease in the peripheral blood flow. Recent studies disclosed the sympathicolytic activity of priscoline.[8,9] Sympathomimetic properties of the drug also

7. Abramson, D. I., and Lichtman, S. S.: Influence of Ergotamine Tartrate upon Peripheral Blood Flow in Subjects with Liver Disease, Proc. Soc. Exper. Biol. & Med. **37**:262, 1937.

8. Bluntschli, H. J., and Goetz, R. H.: The Effect of Ergot Derivatives on the Circulation in Man with Special Reference to Two New Hydrogenated Compounds (Dihydroergotamine and Dihydroergocornine), Am. Heart J. **35**:873, 1948.

9. Grimson, K. S.; Reardon, M. J.; Marzoni, F. A., and Hendrix, J. P.: The Effects of Priscol (2-Benzyl-4,5-Imidazoline HCl) on Peripheral Vascular Diseases, Hypertension and Circulation in Patients, Ann. Surg. **127**:968, 1948.

have been demonstrated.[10] The occasional pressor response observed has been attributed to increased cardiac output overbalancing peripheral vasodilatation. Ergotamine tartrate has a direct constrictor effect on smooth muscle and an inhibiting (vasodilating) effect on the sympathetic nervous system.[8] The latter effect is presumably central in origin and is dependent on the integrity of the sympathetic pathways for its effect. In the normally innervated limb the two actions apparently operate simultaneously, the observed effect depending on which one predominates. It was anticipated that the sympathicolytic action of priscoline® would potentiate the vasodilating effect of ergotamine and reduce the degree of peripheral vasoconstriction. Such an effect was not demonstrated. The likeliest explanation of the observed change appears to be that the amount of priscoline® administered was sufficient to increase cardiac output, thereby elevating the blood pressure further, but insufficiently to overcome the vasoconstriction which increased as a result of a continuation of the effect of the ergotamine.

There was prompt vasodilation as measured by a fall in the blood pressure and an increase in the peripheral blood flow following the intravenous administration of sodium nicotinate. It has been suggested that the vasodilating effect of nicotinic acid and its salts is due to local changes in the blood vessels [11] and that these drugs have an effect similar to that of histamine.[12] The vasoconstrictive action of ergotamine takes place directly on the smooth musculature.[8] It has been shown that warming of an experimental animal does not overcome the vasoconstriction due to the administration of ergotamine [2] and that previous section of sympathetic nerve fibers does not inhibit this vasoconstrictive action.[8] The effective antagonistic action of sodium nicotinate suggests that its vasodilating effect also takes place directly on the effector cells.

The initial clinical response and the later objective observations indicate that in this case sodium nicotinate was an efficient vasodilator in reversing the vasoconstrictive effect of ergotamine tartrate. The degree of the response suggests the continued use of sodium nicotinate as an effective therapeutic agent in this vasoconstrictive state.

SUMMARY AND CONCLUSION

1. A case is reported in which the chronic administration of ergotamine tartrate produced symptoms of vasoconstriction of five months' duration, with complete recovery following withdrawal of the drug and the intravenous injection of 140 mg. of sodium nicotinate.

10. Ahlquist, R. P.; Huggins, R. A., and Woodbury, R. A.: The Pharmacology of Benzyl-Imidazoline (Priscol), J. Pharm. & Exper. Therap. **89**:271, 1947.

11. Abramson, D.; Katzenstein, K., and Senior, F.: Effect of Nicotinic Acid on Peripheral Blood Flow in Man, Am. J. M. Sc. **200**:96, 1940.

12. Popkin, R.: Nicotinic Acid: Its Action on the Peripheral Vascular System, Am. Heart J. **18**:697, 1939.

2. Data on biopsy of muscle, plethysmographic tests and values for skin temperature are presented, showing objective evidence of normal anatomic and physiologic vascular response despite the prolonged vasoconstriction.

3. The administration of priscoline® in the amount used was ineffective in overcoming the vasoconstrictive effect of ergotamine.

4. Sodium nicotinate proved to be an efficient vasodilator in the presence of vasoconstriction due to ergotamine and is suggested as an effective agent in the therapy of this vasospastic state.

5. The absence of tissue necrosis and the demonstration of normal vessels at biopsy tend to support previous observations that intimal change is necessary in ergotism for stasis, thrombosis and tissue necrosis.

Present addresses: W. S. T., 1136 West Sixth Street, Los Angeles; M. L., Cardiovascular Research Unit, Veterans Administration Hospital, Washington, D. C.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

HERMAN BEERMAN, M.D.
LESLIE NICHOLAS, M.D.
MINERVA S. BUERK, M.D.
AND
WILLIAM T. FORD, M.D.
PHILADELPHIA

(Continued from Page 541)

Radioactive Penicillin.—After parenteral administration of penicillin, up to 70 per cent of the drug is excreted unchanged in the urine. In order to determine the fate of the remainder of the penicillin and the excretion path of penicillin after intramuscular and oral administration, Rowlands and his co-workers[182] made urinary excretion studies in female cats, using radioactive penicillin (penicillin containing the radioactive sulfur isotope S^{35}). The radioactivity of the urines was calculated as "Geiger-penicillin units" on the basis that 1,100 disintegrations a minute are equivalent to 1 unit of penicillin. Non-penicillin radioactivity was calculated by subtracting the biologic penicillin level from the Geiger penicillin level. Results demonstrated that after intramuscular injection of labeled penicillin, 72 to 101 per cent of Geiger penicillin was recovered in the urine and only 36 to 66 per cent of biologic penicillin. The authors state that the difference between the amount of penicillin injected and that recovered in the urine as biologic penicillin is represented by radioactive breakdown products of penicillin which are excreted in the urine over the same time interval as penicillin. After oral administration of penicillin, only 24 to 54 per cent of Geiger penicillin was recovered in the urine and 7 to 25 per cent of biologic penicillin. Results based on autopsy of 1 cat showed that 59 per cent of the original radioactivity remained in the gut, while 24 per cent had been recovered in the urine. The authors state that this suggests that nonabsorption from the gut appears to be responsible for the low urinary excretion of penicillin after oral administration.

Procaine Penicillin.—Results of studies on the absorption of procaine penicillin following intramuscular injection and of treatment of

182. Rowlands, S.; Rowley, D., and Stewart, H. C.: Absorption and Excretion Studies with Radioactive Penicillin, Lancet **2**:493-495 (Sept. 25) 1948.

patients with various infections with procaine penicillin in oil are reported by Robinson and his collaborators.[183] Blood levels were determined after intramuscular injection of 300,000 units of procaine penicillin in oil, in oil plus aluminum monostearate and in oil plus sodium carboxymethylcellulose in aqueous suspension. At least 25 patients were studied for each time level indicated. Assayable levels were 0.03 unit per hundred cubic centimeters or higher. Results were as follows: All patients receiving procaine penicillin in oil had assayable levels at twelve, sixteen and twenty hours after injection. Assayable levels were present in 96 per cent at twenty-four hours, 57 per cent at thirty-six hours and 36 per cent at forty-eight hours. Median levels were 0.375 units at twelve and sixteen hours, 0.25 unit at twenty hours, 0.125 unit at twenty-four hours, and 0.031 unit at forty-eight hours. When commercial preparations containing fine particles of procaine penicillin were used, only one third of the patients had assayable levels at twenty-four hours. All patients receiving procaine penicillin in oil plus aluminum monostearate (particles less than 5 microns) had assayable levels at one hundred and twenty hours after injection and 42 per cent at one hundred and forty-four hours. Median levels were 0.25 unit at twenty-four hours, 0.125 unit at forty-eight hours, 0.062 unit at seventy-two and ninety-six hours and 0.031 unit at one hundred and twenty hours. All patients receiving procaine penicillin plus sodium carboxymethylcellulose had assayable levels at sixty hours after injection, and 25 per cent had assayable levels at seventy-two hours. Median levels were 0.5 unit at twelve hours, 0.25 unit at sixteen and twenty hours, 0.125 unit at twenty-four and thirty-six hours and 0.062 unit at forty-eight and sixty hours.

Determinations after injection of 300,000 or 600,000 units of procaine penicillin in oil showed blood levels of at least 0.125 unit at the twelfth hour. Levels were similar with the two doses. Two hundred and fifty-one patients with various infections, including syphilis, were treated with procaine penicillin in oil. Good results were obtained in those with pneumonia, acute bronchitis, acute sinusitis, acute follicular tonsillitis, Vincent's infection, scarlet fever, infectious arthritis, gonorrhea or cellulitis but not in those with typhoid. In 75 cases of primary and secondary syphilis, 600,000 units daily for 5 days, there was healing of lesions and drop in serologic titer in follow-up.

183. Robinson, J. A.; Hirsh, H. L.; Milloff, B., and Dowling, H. F.: Procaine Penicillin: Therapeutic Efficiency and a Comparative Study of the Absorption of Suspensions in Oil and in Oil plus Aluminum Monostearate and of an Aqueous Suspension Containing Sodium Carboxymethylcellulose, J. Lab. & Clin. Med. **33**:1232-1240 (Oct.) 1948.

Robinson [184] determined the blood levels in 110 patients following intramuscular injection of procaine penicillin G (small particle size) suspended in peanut oil with 2 per cent (weight/volume) aluminum monostearate in various dosage schedules and in 40 patients following oral administration of several penicillin preparations. After intramuscular injection of 300,000 units (1 cc.) of the penicillin–aluminum monostearate preparation, average penicillin serum levels were as follows: one hour, 0.184 unit; two hours, 0.161 unit; four hours, 0.507 unit; eight hours, 0.121 unit; twenty-four hours, 0.23 unit; forty-eight hours, 0.123 unit; seventy-two hours, 0.078 unit; ninety-six hours, 0.07 unit, and one hundred and twenty hours, 0.055 unit. Therapeutic levels (0.03 unit per hundred cubic centimeters or more) were maintained for seventy-two hours in 90 per cent of cases, and one hundred and twenty hours in 70 per cent of cases. Repeated injections at twelve and twenty-four hour intervals for five successive days gave levels five to thirty times the minimum level for twelve and twenty-four hours, respectively, after the last injection. Injection of 600,000 units every twenty-four hours for five successive days gave levels eight times the minimum level at one hour after injection and maintained therapeutic levels for twenty-four hours after the last injection. Serum levels were usually lower in active and moderately active patients than in sedentary patients. Oral administration of 100,000 units of crystalline procaine penicillin with aluminum monostearate buffered with calcium carbonate gave adequate levels for eight hours. Levels were in general lower than those obtained with three oral penicillin preparations of crystalline penicillin buffered with calcium carbonate or trisodium citrate. Doses of 500,000 and 1,000,000 units of crystalline penicillin, both buffered and unbuffered, gave adequate levels (0.03 unit) for sixteen hours.

Hewitt and his co-workers [185] present pharmacologic data concerning the use in man of crystalline procaine penicillin G suspended in oil. The following single intramuscular injections were employed: 1 cc. of procaine penicillin G in oil (300,000 units per cubic centi-

184. Robinson, J. M.: Procaine Penicillin with Aluminum Monostearate: Serum Concentrations After Oral and Intramuscular Administration, J. Michigan M. Soc. **48**:337-342 (March) 1949. Robinson, J. M.; DeZelia, D., and Kalish, S.: Serum Levels Using Procaine Penicillin with Aluminum Monostearate: Oral and Intramuscular Administration, Proceedings of Detroit Physiological Society, ibid. **48**:217 (Feb.) 1949.

185. Hewitt, W. L.; Whittlesey, P., and Keefer, C. S.: Serum Concentrations of Penicillin Following Administration of Crystalline Procaine Penicillin G in Oil, New England J. Med. **239**:286-290 (Aug. 19) 1948. Whittlesey, P., and Hewitt, W. L.: Serum Concentrations of Penicillin Following Administration of Crystalline Procaine Penicillin G in Aqueous Suspension, Proc. Soc. Exper. Biol. & Med. **68**:658-661 (July-Aug.) 1948.

meter) and 2 cc. of procaine penicillin G in oil (300,000 units per cubic centimeter). Persons without evidence of impaired cardiac, renal or hepatic function served as subject of the tests. The majority were women who had passed through labor or young men who had recovered from acute illness. In a number of cases the preparations were employed in the treatment of various acute illnesses as the definitive form of therapy. It was found that the maximum serum penicillin concentrations obtained with procaine penicillin G in oil were distinctly lower than those following similar doses of sodium penicillin G in peanut oil and beeswax. The concentrations following administration of the former preparation, particularly with a dose of 600,000 units, showed considerably more uniformity throughout the twenty-four hours following injection. A comparison of the serum penicillin concentrations obtained after a dose of 300,000 and 600,000 units of procaine penicillin G revealed the most characteristic difference to be a prolongation of a given effective penicillin level rather than an increase in the magnitude of the penicillin concentration during the early period after administration. Crystalline procaine penicillin G in oil was superior to crystalline sodium penicillin G in peanut oil and beeswax for maintaining an effective serum penicillin concentration for twenty-four hours after injection.

Injections of procaine penicillin in oil, in water and in oil incorporated with aluminum monostearate, containing 300,000 units per millimeter were given to 185 patients by Young, Andrews and Montgomery.[186] Procaine penicillin G in oil with aluminum monostearate was superior to other preparations tested for delayed absorption of penicillin. It is a stable preparation, is easy to administer, causes no pain or side effects and in doses of 300,000 units gave therapeutic blood penicillin levels for twenty-four hours in virtually 100 per cent of patients tested. Tests with oil and water suspensions of procaine penicillin without aluminum monostearate show that with a dose of 600,000 units 100 per cent of patients had a therapeutic level at the end of twenty-four hours; with a dose of 300,000 units, however, only 50 to 60 per cent had this level. A few patients received a single dose of 2,000,000 units of procaine penicillin with aluminum monostearate in oil, and most had a therapeutic blood level for a week after injection. A preparation of procaine penicillin in oil with aluminum monostearate together with soluble penicillin combined the advantages of rapid initial absorption and the following delayed action. Procaine penicillin G in oil with aluminum monostearate is the most suitable preparation for clinical use when economy in material, slow absorption and a long-lasting therapeutic blood penicillin level are important.

186. Young, M. T.; Andrews, G. W. S., and Montgomery, D. M.: Procaine Penicillin, Lancet **1**:863-865 (May 21) 1949.

Oral Administration of Procaine Penicillin: Kitchen, Thomas and Rein,[187] using single oral doses of crystalline sodium penicillin G (1,060,000 units and 530,000 units) and crystalline procaine penicillin G (550,000 units), studied the serum concentration by a cup plate method, utilizing Sarcina lutea as the test organism. They demonstrated that crystalline procaine penicillin G appeared in the serum in a much lower concentration and disappeared more rapidly than did crystalline sodium penicillin G.

Depot Effect of Procaine Penicillin Suspensions: Essellier[188] and his co-workers determined the penicillin titer in the serum of 59 afebrile persons with normal kidneys, in 10 febrile patients and in 7 afebrile patients with renal insufficiency to whom intramuscular injections of a procaine salt of penicillin G in sesame oil were given. In 20 of the 59 persons after one injection of 1 cc. of a suspension of 300,000 units of this preparation an effective therapeutic concentration of penicillin (a level above 0.03 unit per cubic centimeter) was obtainable on an average for thirty hours with extreme duration values of fifteen to over thirty-six hours. In 14 patients after one injection of 400,000 units of the drug a prolongation of the action of the drug was not obtained, while in 8 patients after one injection of 600,000 units of the drug the duration of its action was prolonged to forty-eight hours. In the 10 febrile patients and in the 7 afebrile patients with renal insufficiency after one injection of 300,000 units of the drug the same effective therapeutic concentration of penicillin was obtainable on an average for over thirty-six hours, with extreme duration values of twenty-one to over thirty-six hours in the first group and of thirty to over forty-eight hours in the second group.

A series of in vivo and in vitro studies were conducted by Hobby, Brown and Patelski[189] with procaine penicillin G and procaine penicillin dihydro-F of known potencies. The in vitro studies were made on broth cultures of hemolytic streptococci, D. pneumoniae, Staph. aureus, B. subtilis, green-forming streptococci, Esch. coli and A. aerogenes diluted to a constant density and tested for inhibition of growth by varying quantities of penicillin. These studies indicate that crystalline procaine penicillin G and procaine penicillin dihydro-F are highly

187. Kitchen, D. K.; Thomas, E. W., and Rein, C. R.: Serum Concentration Following the Oral Administration of Crystalline Procaine Penicillin G and Crystalline Sodium Penicillin G, J. Invest. Dermat. **12**:147-149 (March) 1949.

188. Essellier, A. F.; Koszewski, B. J., and Gundersen, F. O.: Investigation on Depot Effect of Oil Procaine Penicillin Suspensions, Schweiz. med. Wchnschr. **78**:1001-1004 (Oct. 16) 1948.

189. Hobby, G. L.; Brown, E., and Patelski, R. A.: Biological Activity of Crystalline Procaine Penicillin in Vitro and in Vivo, Proc. Soc. Exper. Biol. & Med. **67**:6-14 (Jan.) 1948.

effective antibacterial agents in vitro and in vivo. Crystalline procaine penicillins G and dihydro-F in oil when given intramuscularly to rabbits in doses of 30,000 units per kilogram produce detectable blood levels for twenty-four to thirty hours or longer. In man a single injection of 300,000 units of crystalline penicillin G in oil may produce detectable blood levels lasting from twenty-four to forty-eight hours, while penicillin may be excreted forty-eight to sixty hours. Crystalline procaine penicillin has a low toxicity index in animals. Other water-insoluble salts of penicillin when suspended in oil produce marked prolongation of the blood levels.

The effect of single daily injections of procaine penicillin was studied by Jones and Shooter.[190] They used five daily injections of 1 cc. (300,000 units) of procaine penicillin G in peanut oil. The subjects studied were 45 ambulant patients and 4 ward patients with various acute localized infections and ranging in age from 17 to 83 years. Penicillin blood levels were determined by the Oxford slide method, with use of the Oxford H Staphylococcus, approximately twenty-four hours after each injection or immediately before the next injection. At times varying from eighteen to twenty-six hours after the first injection of 300,000 units of procaine penicillin it was possible to detect penicillin in the blood of 37 of 45 patients. Determinations made between nineteen and twenty-six hours after the second and subsequent daily injections showed detectable amounts of penicillin in 93 of 109 patients.

Wilson, Farquhar, and Lewis[191] tried to assess the value of procaine penicillin in treatment of infants and children by estimating blood levels of penicillin following a single injection. The preparation used in this clinical study was a suspension of procaine penicillin G in peanut oil in which 64.5 per cent of the particles were less than 50 microns in diameter and 34.5 per cent were larger than 50 microns. Several groups of children were segregated into age groups from premature to 9 years. Each group was given a single injection varying from 60,000 units for premature infants to 300,000 units for 9 year children. Capillary blood was taken at appropriate intervals, for determination of penicillin levels. No untoward reactions were reported. In premature and young infants who received a total dose of 30,000 units per kilogram the highest blood level was 2½ to 25 units per cubic millimeter, which was usually maintained for twelve hours, and after forty-eight hours the majority of young infants had a perceptible blood level. Infants from 1 to 12 months receiving 16,000

190. Jones, P. F., and Shooter, R. A.: Procaine Penicillin: Effect of Single Daily Injections, Brit. M. J. **2**:933-934 (Nov. 27) 1948.

191. Wilson, W. M.; Farquhar, J. W., and Lewis, I. C.: Procaine Penicillin in Infants and Children, Lancet **1**:866-868 (May 21) 1949.

units per kilogram showed a blood level peak of 1 to 5 units; the level fell rapidly, but a therapeutic level was maintained for the majority of cases in twenty-four hours. In the presence of renal damage, the levels remained persistently high. It is suggested that procaine penicillin may be of especial value in pyogenic diseases. It is advisable not to combine use of procaine penicillin and sulfonamides until more is known of the antagonism between procaine and sulfanilamide.

Kitchen, Thomas and Rein [192] studied the concentration of penicillin in human serum following the intramuscular injection of procaine penicillin (fine particle size) in oil with 2 per cent aluminum monostearate. This product was administered in five different schedules of treatment: (1) 1,200,000 units (4 cc.) in one depot; (2) 2,400,000 units (8 cc.) in one depot; (3) 2,400,000 units (4 cc. plus 4 cc.) in two depots; (4) 300,000 units (1 cc.) every day for fifteen days; (5) 300,000 units (1 cc.) every other day for fifteen days. The first three schedules are being employed in the treatment of syphilis. Assays were performed by a cup plate method utilizing S. lutea as the test organism. With each of these schedules the serum concentration remained above 0.03 unit per cubic centimeter of blood serum (theoretic minimum therapeutic level) for eight days. Results with the last two schedules show that the blood concentration is definitely cumulative in direct proportion to the frequency of the administration of the product.

Buckwalter and Dickison [176] introduced the principle of suspending penicillin salts in peanut oil jelled with an aluminum monostearate to form a water-repellent substance. They compared the absorption-delaying properties of this vehicle with the conventional repository vehicles in animals. Thomas and his colleagues [193] compared the blood levels in human subjects following the administration of the newer type absorption-delaying mediums, i. e., penicillin salts in peanut oil (jelled with aluminum monostearate) with the conventional repository vehicles, i. e., penicillin salts in oil and wax. Assays were performed by two methods: (1) a modified Rammelkamp method and (2) a cup plate procedure using S. lutea. Control samples of blood were drawn before injection. Each patient received 300,000 units of penicillin in repository form. Consecutive blood samples were taken at varying intervals: one, twelve, twenty-four, thirty, thirty-six, forty-eight and seventy-two hours. In this study the following products were tested: (1) sodium penicillin

192. Kitchen, D. K.; Thomas, E. W., and Rein, C. R.: Serum Concentrations Following Five Treatment Schedules with Procaine Penicillin in Oil with Aluminum Monostearate, J. Invest. Dermat. **12**:111-115 (Feb.) 1949.

193. Thomas, E. W.; Lyons, R. H.; Romansky, M. J.; Rein, C. R., and Kitchen, D. K.: Newer Repository Penicillin Products, J. A. M. A. **137**:1517-1519 (Aug. 21) 1948.

G in peanut oil with 4.8 per cent (weight/volume) white wax; (2) sodium penicillin G in peanut oil with 2 per cent (weight/volume) aluminum monostearate; (3) procaine penicillin G in oil; (4) procaine penicillin G in peanut oil with 2 per cent (weight/volume) aluminum monostearate (large particle); (5) aluminum penicillin in peanut oil with 2 per cent (weight/volume) aluminum monostearate; (6) procaine penicillin G in peanut oil with 2 per cent (weight/volume) aluminum monostearate (small particle). After a four to six hour interval there were 86.7 per cent of patients receiving procaine penicillin G in peanut oil with 2 per cent aluminum monostearate (small particle) who had blood levels of 0.03 unit per cubic centimeter, or higher. After forty-eight hours 96.9 per cent of this group had blood levels of 0.03 unit or higher. Procaine penicillin G in peanut oil with 2 per cent aluminum monostearate (large particle) ranked second in maintenance of blood level, 52 per cent having blood levels more than 0.03 unit per cubic centimeter at forty-eight hours. Sodium penicillin G in peanut oil with 2 per cent aluminum stearate was the third most effective medium. Aluminum penicillin in peanut oil with 2 per cent aluminum monostearate, sodium penicillin G in peanut oil with 4 per cent white wax and procaine penicillin G in oil followed in order of effectiveness. In order to determine any untoward effects of repeated injection and to record maintenance of blood concentration, 16 patients were given daily for sixteen days 300,000 units of large particle procaine penicillin per cubic centimeter of peanut oil jelled with 2 per cent aluminum monostearate. Daily blood levels were determined on this group at twenty-four hour intervals. All these patients had a daily blood level of over 0.03 unit per cubic centimeter. The results of this work indicate that the absorption of all salts of penicillin tested was delayed longer in the aluminum monostearate in peanut oil gel than when the same salts were suspended in peanut oil alone or in peanut oil plus wax. Further, it is of particular interest to note that procaine penicillin in peanut oil jelled with 2 per cent aluminum monostearate of a small particle size maintained a blood level concentration over a longer period than the same combination but with penicillin of large-sized particles. No instance of undue irritation or of untoward effects was reported by or observed in any of the subjects receiving penicillin jelled with aluminum monostearate in peanut oil, other than the occasional allergic reaction to penicillin. The influence of particle size per se on the maintenance of blood concentration will be reported later by Buckwalter, Dickison and this group.

Boger and his associates [194] show that penicillin levels of the cerebrospinal fluid level were greatly enhanced by the oral administration

194. Boger, W. P.; Baker, R. B., and Wilson, W. W.: Therapeutic Concentrations of Penicillin in the Cerebrospinal Fluid Following Parenteral Penicillin and Oral Caronamide, Tr. Am. Neurol. A. **73**:105-107 1948.

of carinamide. With penicillin therapy alone, 18 out of 23 patients with dementia paralytica had penicillin concentrations in the cerebrospinal fluid ranging from 0.019 to 0.052 unit per cubic centimeter. After the combined penicillin and carinamide therapy, 20 of 25 patients had penicillin concentrations ranging from 0.052 to 2.5 units per cubic centimeter of cerebrospinal fluid. In a later publication Boger and Wilson [195] report on the penicillin levels in the cerebrospinal fluid of 21 patients with central nervous system syphilis (dementia paralytica). The penicillin was administered intravenously in order to obtain the advantage of a brief but high concentration of penicillin in the plasma immediately after administration. This might favor diffusion across the blood-brain barrier. Penicillin in aqueous solution (500,000 units) was given intravenously, and thereafter blood specimens were drawn at five minutes, two hours and three hours. In addition, at the two and three hour periods a lumbar puncture was performed to obtain cerebrospinal fluid for penicillin assay. Both the blood and the cerebrospinal fluid specimens were assayed for penicillin by a modified Rammelkamp serial dilution method, employing a group A hemolytic streptococcus as the test organism. Three patients were studied in this manner after the administration of 500,000 units of penicillin alone, and 3 received the same dose of penicillin and 3 Gm. of carinamide intravenously in aqueous solution. An additional 15 patients were investigated twice, first with penicillin alone and then seven to twenty-seven days later with penicillin and carinamide in the same dosage as noted previously. Boger and Wilson found that the administration of 500,000 units of penicillin in aqueous solution resulted in demonstrable concentrations of penicillin in the cerebrospinal fluid at two hours in 14 of 18 patients and at three hours in 15 of 18 patients. When the same dose of penicillin was administered with 3 Gm. of carinamide, penicillin appeared in the cerebrospinal fluid at two and three hours in all 18 patients. The plasma concentrations resulting from the administration of penicillin were enhanced by carinamide from two to five times, and the cerebrospinal fluid concentrations were doubled.

Histopathologic Aspects of Dementia Paralytica Following Penicillin.—Smith and de Morais [196] reported the cases of 4 patients with dementia paralytica who died some weeks after parenteral treatment with total doses between 2,400,000 and 4,800,000 units of penicillin.

195. Boger, W. P., and Wilson, W. W.: Rapid Attainment of Therapeutic Penicillin Concentrations in the Cerebro-Spinal Fluid, Am. J. M. Sc. **217**:593-599 (June) 1949.

196. Smith, R. H. F., and de Morais, V.: Histopathological Findings in General Paresis After Penicillin Treatment: Report on Four Cases, J. Ment. Sc. **94**:70-76 (Jan.) 1948.

Two of the patients had improved clinically as well as serologically. Histologic examination of the brains of these 2 patients revealed inflammatory changes which were distinctly less intense than in untreated patients with dementia paralytica. The iron reaction was positive in all patients, but it was least intense in the 2 patients who had improved. The exacerbation of mental symptoms seen on the eighth day of treatment in 1 of these 2 patients was presumably a Herxheimer reaction. No spirochetes were found in any of the four brains. These observations closely resemble those noted after treatment with malaria. In the 2 cases in which there was no improvement the condition was of the juvenile type. One of the patients, a woman aged 27, died thirty days from the start of treatment, after rapidly deteriorating both mentally and physically. The second patient, a youth of 20, showed no improvement during and after treatment with penicillin. He gradually deteriorated, both mentally and physically, and died sixty-six days from the start of treatment. Histologic studies in these 2 cases showed no mitigation of the inflammatory reaction. The 2 cases in which there was improvement suggest that treatment with penicillin alone is capable of influencing the pathologic progress of dementia paralytica.

Therapeutic Effect of Penicillin.—Boak and Carpenter [197] studied the effects of penicillin G on five strains of T. pallidum, maintained by animal passage in rabbits for from six months to thirty-four years, in order to determine whether a variation in the resistance of strains of T. pallidum to penicillin G might explain in part why the drug will not cure a greater percentage of patients with syphilis. The Nichols strain, isolated from spinal fluid in 1912, the Zinsser-Hopkins strain recovered from a mucous patch in 1913 and three other strains ("All." "Ama" and "Ami"), obtained recently from penile chancres by intratesticular inoculation of rabbits, were employed in this study. Five groups of 10 rabbits each were inoculated intratesticularly with the five different strains of treponemes which had been well adapted to the rabbit. Approximately six weeks after inoculation the animals showed typical lesions of experimental syphilis which were positive for treponemes on dark field examination. They were then treated with a single lot of crystalline penicillin G. Each group of 10 animals received a total dose of 500, 1,000, 2,000, 4,000 or 8,000 units per kilogram of body weight. The penicillin was administered in divided doses intramuscularly every four hours for twenty-four injections. The Nichols strain required the greatest amount of penicillin per kilogram of body weight to effect a cure. The median curative dose for this

197. Boak, R. A., and Carpenter, C. M.: The Therapeutic Efficacy of Penicillin G in Experimental Syphilis Produced by Five Different Strains of Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **33**:8-11 (Jan.) 1949.

strain was 2,520 units per kilogram of body weight. The median curative dose per kilogram of body weight for the Zinsser-Hopkins strain was 1,570 units. "All" and "Ama" strains possessed approximately the same degree of sensitivity to the drug. The median curative dose for each was, respectively, 1,420 and 1,210 units per kilogram of body weight. Strain "Ami" was the least resistant to penicillin. The median curative dose was only 500 units per kilogram of body weight. The variation in the median curative dose of penicillin G per kilogram of body weight in experimental syphilis produced by five strains of T. pallidum suggests that their sensitivities to a single lot of the drug were considerably different. Neither the length of time that a strain had been maintained by animal passage in rabbits nor the number of passages appeared to be the significant factor responsible for the variation in the sensitivity of the strains to penicillin. A comparison of the resistance of strain "All," recovered in 1938, with that of strain "Ami," recovered in 1939, subjected to sixteen and fourteen animal passages, respectively, showed the median curative doses of each to be widely different, namely, 1,420 and 500 units of penicillin G per kilogram of body weight. On the other hand, strain "Ama," isolated only six months prior to this study and subjected to only four animal passages, required 1,210 units of penicillin G per kilogram of body weight for its median curative dose. Only one strain, "Ama," could have had contact with penicillin prior to isolation by animal inoculation. The other four strains were recovered from patients prior to the clinical use of penicillin in syphilis. The authors state that some of the discrepancy in the median curative doses for these strains may be due to experimental error. On the other hand, the therapeutic efficacy of penicillin in experimental syphilis produced by the Nichols strain was determined by several investigators and a remarkable degree of uniformity in results was achieved.

Rosahn and his colleagues [198] studied the effect of sodium penicillin and of crystalline penicillins F and X in experimental rabbit syphilis, and compared their results with results already reported for penicillins G and K. The median curative dose (CD/50), which is defined as that amount of the drug required to cure 50 per cent of the animals, was calculated for the three kinds of penicillin under investigation. The following values for the median curative doses were obtained: sodium penicillin 2,375 units per kilogram; penicillin F 8,000 units and penicillin X 4,400 units. Crystalline penicillin G, when tested by Carpenter and Boak and by Fleming, had a CD/50 value of approxi-

198. Rosahn, P. D.; Gueft, B., and Rowe, C. W.: Therapeutic Efficacy of Sodium Penicillin and of Penicillins F and X in Experimental Rabbit Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:317-326 (July) 1948.

mately 1,500 units per kilogram. Mahoney, Arnold and Chesney checked crystalline penicillin K and determined a CD/50 of 16,000 units per kilogram. A comparative assay of the effectiveness of these penicillins gave results of the following order: G — 100, X — 34, F — 19, K — > 9. Thus, penicillins F and X were observed to be in intermediate positions between penicillin G, the most potent preparation, and penicillin K, the least potent, while sodium penicillin was seen as relatively more effective than penicillin F, X or K.

Methods of Administration.—Discontinuous Therapy: This study was conducted in the Cornell–New York Hospital medical service and the Cornell Division of Bellevue Hospital by Tompsett and his group.[199] The first part of the study is a comparison of clinical results obtained with continuous and discontinuous therapy in uncomplicated pneumococcic pneumonia. The discontinuous dosage schedule consisted of 300,000 units of crystalline sodium penicillin G in 1 cc. of isotonic sodium chloride solution administered intramuscularly. On the first day the patient received two doses at twelve hour intervals. On the second and third days a single dose was given. The continuous dosage schedule consisted of single daily injections of 300,000 units of procaine penicillin which was shown in previous studies to provide a continuous low serum concentration of 0.3 unit per cubic centimeter of serum. In the first portion of the study 39 patients with clinical pneumonia received its discontinuous therapy schedule. Nineteen of these patients had pneumococcic pneumonia proved bacteriologically. In 2 of these patients meningitis developed which failed to respond to intensive therapy. In comparison 32 patients received continuous therapy. Twenty-one of these had proved pneumococcic pneumonia. In this group, 1 developed or had an undetected empyema at onset of therapy, while a second patient failed to respond and died. Composite temperature charts of the patients in each group under these schedules of therapy were identical with those treated earlier with 20,000 units of aqueous penicillin intramuscularly every two or three hours. Temperatures returned to normal within a twenty-four hour period after institution of therapy. Clinically it was impossible to distinguish any difference in the classic results obtained by the two aforementioned schedules. The second portion of the study was devoted to the treatment of miscellaneous infections with the discontinuous therapy regimen. The over-all results were satisfactory, with only one fatality due to cardiac failure and uremia. It is the opinion of the authors that discontinuous administration of penicillin may not be as effective as intensive continuous therapy in the prevention of nonsuppurative

199. Tompsett, R.; Timpanelli, A.; Goldstein, O., and McDermott, W.: Discontinuous Therapy with Penicillin, J. A. M. A. **139**:555-560 (Feb. 26) 1949.

complications, such as infections due to group A hemolytic streptococci. It is emphasized that suppurative complications may occur more frequently in patients receiving the discontinuous therapy than in those patients receiving continuous therapy. Nevertheless, the clinical results indicate that highly effective penicillin therapy may be provided by the discontinuous method.

Oral Administration: Results obtained by Starkey and Dixon [200] with the oral administration of amorphous penicillin in eggnog with or without the addition of sodium bicarbonate indicate that effective and sustained levels are possible by this procedure.

In the treatment of experimental syphilis in rabbits, Kolmer [201] demonstrated a synergistic or additive activity of orally administered penicillin and intravenously administered oxophenarsine hydrochloride, orally administered penicillin and intramuscularly administered oxophenarsine hydrochloride and orally administered penicillin and intramuscularly administered bismuth subsalicylate. In each instance not completely curative doses were used in the combinations noted, and complete cure was obtained.

Endermic Administration: Comèl,[202] of the University of Pisa, used small intradermal injections of penicillin in oil and wax. Comparative studies show that 10,000 to 20,000 units of penicillin is much more active by the endermic route than by the intramuscular or subcutaneous routes. A larger and more prolonged effect is attained by the use of the slowly absorbed excipient. From thirty to thirty-five daily injections of 20,000 units of penicillin in oily suspension are effective in making syphilitic lesions disappear and the serologic reaction to become negative. Some immediate, delayed, recurring and late reactions have been encountered. Bismuth compounds given in the same circumstances yield good results. One wonders, however, whether this procedure does not increase the risk of reaction generally.

EARLY SYPHILIS

Penicillin.—The place of penicillin in the therapy of early syphilis is gradually being crystallized. While there are still differences of opinion regarding effective time-dose relationships, there is continued agreement

200. Starkey, H., and Dixon, J. H.: Oral Administration of Penicillin, Canad. M. A. J. **59**:47-50 (July) 1948.

201. Kolmer, J. A.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: IV. The Synergistic or Additive Activity of Penicillin by Oral Administration with Oxophenarsine Hydrochloride ("Mapharsen") by Intravenous and Intramuscular Injection and Bismuth Subsalicylate by Intramuscular Injection, Arch. Dermat. & Syph. **57**:965-974 (June) 1948.

202. Comèl, M.: Results of Endermic Therapy of Venereal Diseases, Dermatologica **96**:377-381, 1948.

as to the safety and relative effectiveness of penicillin alone or, as noted elsewhere, with metal or fever therapy. The largest experience with penicillin therapy continues to be an American achievement.

Altshuler, Karpinos, Leifer and Ozog [203] undertook an extensive study to determine the therapeutic efficacy of the penicillin schedule used in the Army for the treatment of early syphilis, consisting of 60 consecutive intramuscular injections of 40,000 units of aqueous amorphous penicillin at three-hour intervals for a period of seven and one-half days, amounting to a total dose of 2,400,000 units. In an effort to determine the influence of changes in the proportion of G, F, X and K species in amorphous penicillin on the therapeutic outcome, the patients were separated on the basis of the period of treatment into those initially treated between (1) June 1 and Dec. 31, 1944, (2) Jan. 1 and June 30, 1945, and (3) July 1 and Dec. 31, 1945. The data of each of the three groups were separated into primary seronegative, primary seropositive and secondary syphilis and by race. The material for the study was obtained from syphilis registers. No patient was considered to have attained therapeutic success unless at least six months of follow-up after initial treatment had indicated cure. Soldiers in whom new syphilitic lesions developed at any time after completion of their initial treatment were classified as having infectious relapse, the possibility of reinfection being disregarded. Those with seronegative primary syphilis were classified as showing serologic relapse whenever the serologic test elicited a doubtful or positive reaction after six months of follow-up. Those with seropositive primary and secondary syphilis were not considered to have had therapeutic failure even though the serologic reactions had not become negative before the termination of the six month follow-up period, but they were regarded as having had serologic relapses if the serologic reaction had been recorded at any time as doubtful or negative and subsequently as positive. Those with seropositive primary and secondary syphilis who showed doubtful or positive reactions after the completion of six months of follow-up were classified as seroresistant. A doubtful or definitely abnormal spinal fluid placed the soldier in the category of failure, as did symptomatic evidence of neurosyphilis or of any other form of clinical relapse. Every soldier who had been retreated for any reason whatsoever was considered a failure. Thus, patients who had been observed for less than six months after treatment were considered as making satisfactory progress provided (1) no infectious or other form of clinical relapse had occurred, (2) no serologic relapse had occurred,

203. Altshuler, L.; Karpinos, B. D.; Leifer, W., and Ozog, J. J.: Efficacy of Penicillin Treatment in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:126-138 (March) 1949.

(3) there was no record of retreatment for any reason and (4) there was no record of an abnormal spinal fluid. All such cases in which the patients had had less than six months of follow-up were classified as incomplete.

A total of 30,972 patients from syphilis registers comprised this study (17,652 white and 13,320 Negro). Of these, 22,065 patients were observed for less than six months and 8,907 patients had a follow-up of six months or more. The failure rates of early syphilis were influenced by the stage of infection at the time of initial treatment, by the patient's race and by the time period during which the treatment was administered. The lowest failure rate was obtained for patients with seronegative primary syphilis (87.3 per 1,000 patients of both racial groups), a higher one for patients with seropositive primary syphilis (186.2 per 1,000 patients) and the highest for patients with secondary syphilis (282.7 per 1,000 patients). The total failure rate was 159.1 per 1,000 treated patients. This held true for each of the three periods of treatment and for both white and Negro patients. The comparatively more satisfactory results for the entire group can be ascribed to the fact that 43.8 per cent of the patients were in the seronegative primary phase, 42.2 per cent in the seropositive primary phase and only 14 per cent in the secondary phase. Such a high proportion of cases of primary syphilis is seldom encountered in civil clinics.

The failure rate was consistently higher among Negro than among white patients. This held true for each stage of infection and each period of treatment. The total failure rate was 100.5 per 1,000 white and 227.0 per 1,000 Negro patients. The higher incidence of failures among Negroes has been attributed to their higher incidence of reinfections. All new syphilitic lesions that appeared after initial treatment were classified as infectious relapses, disregarding reinfections. While there was unquestionable evidence of more reinfections among Negroes, the lack of difference between the distributions of failures among white and Negro patients by type of failure seems to indicate that other factors may contribute to the higher failure rates for Negroes.

The failure rate increased during the period, irrespective of the phase of syphilis or the racial group. The lowest failure rate was observed from June 1 to Dec. 31, 1944, and the highest was seen from July 1 to Dec. 31, 1945. The most striking increase in the failure rate occurred in the third period of treatment. The rate for the last six months of 1945 was about 86 per cent greater than that for the last seven months of 1944. These observations suggest that the increase in the ineffective K and a proportionate decrease in the active species G of the penicillin, which resulted in a loss of therapeutic potency,

occurred in 1945, probably toward the middle of that year. At present there is no concern over this situation, since crystalline penicillin G has almost completely replaced the amorphous variety, and, even when the latter variety is produced, its G content is probably greater than 85 per cent. The findings reported clearly indicate the beneficial effect of penicillin on abnormal spinal fluid, resulting in a low percentage of patients with asymptomatic neurosyphilis. Among the 5,600 patients for whom the results of examination of the cerebrospinal fluid were available, only 3 had doubtful and 21 had abnormal spinal fluids (0.4 per cent). This seems to indicate a remarkable neurotropic effect of penicillin.

In evaluation of the penicillin therapy of early syphilis, Thomas [204] points out that the available data are limited to the use of aqueous solutions and penicillin in oil and wax. In the treatment of syphilis the height of the penicillin blood levels appears to be of little significance, since T. pallidum is destroyed by very low concentrations. Duration of treatment appears to be more important than dosage. The optimum period of treatment for early syphilis seems to be at least fifteen days. Best results so far have been obtained with 300,000 to 600,000 units of penicillin in oil and wax daily for fifteen days. With penicillin in aqueous solution results have been as good with a total dose of 2,400,000 units with individual injections every two to four hours for four to seven and one-half days as with a total dose of 5,000,000 units. The failure rate with both penicillin in aqueous solution and penicillin in oil and wax has been about 20 per cent. However, 40 to 50 per cent of failures were probably reinfections. The introduction of procaine penicillin G in oil and 2 per cent aluminum monostearate promises to simplify the treatment of early syphilis. A single injection of 300,000 units has given demonstrable blood levels for four days in most cases, 1,200,000 to 2,400,000 units for five to seven days. Suggested schedules for this preparation are (1) two injections of 1,200,000 units each a week apart and (2) 600,000 units twice a week for two or three weeks. For retreatment of failures a total dosage of 6,000,000 units of penicillin in not less than fifteen days is suggested. The addition of arsenicals or bismuth is not considered advantageous except in cases in which the disease may prove to be resistant to penicillin. Patients should be observed for two years after treatment. In about 75 per cent of successfully treated patients the disease became seronegative within six months after treatment. The remaining 25 per cent had low reagin titers after six months. Such patients do not require retreatment unless the titers show evidence of relapse or reinfection.

204. Thomas, E. W.: Penicillin Treatment of Early Syphilis, Am. J. Med. 5:687-692 (Nov.) 1948.

Walker and Utterback,[205] with the aid of 10 collaborating authors, present the follow-up study of 159 patients who were treated between November 1943 and June 1944 for dark field–positive primary and secondary syphilis.

Merrell [206] reports the results of a statistical analysis of 7,000 patients with early syphilis treated with amorphous penicillin.

Rider,[207] in the second part of the report on the results of the nationwide study, compared the results obtained with amorphous penicillin with crystalline penicillin G and with aqueous penicillin in oil and wax based on cumulative failure rates. In schedules employing 2,400,000 units in four, seven and one-half and fifteen days, if clinical failure rates only are included, no very marked differences in effectiveness between the amorphous and the crystalline G appear. If serorelapses and cases of seroresistance in which clinical failure was not observed are added to the cases of clinical failure, there is a marked difference between the two penicillins in favor of G. The same results were obtained in the 4,800,000 unit schedules. Thus, up to the fourteenth month following treatment, crystalline penicillin G in quantities of 2,400,000 or 4,800,000 units over a seven and one-half day period at the rate of an injection every two or three hours gives results superior to those obtained with amorphous penicillin in comparable dosages. Rider also reaffirms the idea that penicillin in oil and wax is at least as effective in the treatment of early syphilis as penicillin in aqueous solution.

Reynolds [208] made a statistical comparison to determine the cause of discrepancies between the results of the Venereal Disease Research Laboratory and those of the Central Statistical Unit in the penicillin treatment of early syphilis. In order to make this comparison Reynolds reviewed data from the Venereal Disease Research Laboratory, United States Marine Hospital, Staten Island, N. Y., and the Central Statistical Unit at Johns Hopkins Hospital. They observed that variation in statistical analysis of results obtained in treatment of early syphilis with penicillin by the Venereal Disease Research Laboratory and the

205. Walker, A. E., and Utterback, M.: Treatment of Early Syphilis with Small Doses of Crude Penicillin, Arch. Dermat. & Syph. **59**:277-283 (March) 1949.

206. Merrell, M.: Results of the Nationwide Study of Penicillin in Early Syphilis: I. Amorphous Penicillin in Aqueous Solution, Am. J. Syph., Gonor. & Ven. Dis. **33**:12-18 (Jan.) 1949.

207. Rider, R. V.: Results of the Nationwide Study of Penicillin in Early Syphilis: II. Amorphous Penicillin Versus Crystalline Penicillin G, and Aqueous Penicillin Versus Penicillin-Oil-Beeswax, Am. J. Syph., Gonor. & Ven. Dis. **33**:19-26 (Jan.) 1949.

208. Reynolds, F. W.: Penicillin in Early Syphilis: A Statistical Comparison of Results from Two Studies. J. Ven. Dis. Inform. **29**:272-277 (Sept.) 1948.

Central Statistical Unit are based on differences in (1) definition of terms, (2) sex and race, (3) stage of disease, and (4) follow-up.

Reynolds [209] also presents an evaluation of penicillin therapy in early syphilis based on the results obtained in the two cooperative nationwide studies (Syphilis Study Section, National Institutes of Health, and Venereal Disease Division, United States Public Health Service). Penicillin is evaluated according to the following criteria for an ideal therapeutic agent for syphilis: (1) completely and uniformly effective; (2) entirely devoid of toxicity; (3) readily administered with a minimum of inconvenience to the patient and the physician. The author states that after five years of use there have been no fatalities and few serious reactions attributable to penicillin. The most frequent untoward reaction is allergic dermatitis. Crystalline penicillin G appears to be less allergenic than less pure preparations. With increased use of penicillin, the incidence of allergic reactions has increased. Procaine penicillin appears to cause less dermal sensitization than earlier developed types of penicillin. Jarisch-Herxheimer reactions occur in about half of the patients. The Milian type of reaction has not been reported. The cooperative studies have revealed the following facts concerning the therapeutic efficacy of penicillin: 1. Penicillin alone is somewhat inferior to properly administered metal chemotherapy. 2. Crystalline penicillin G is superior to amorphous penicillin. 3. Therapeutic results with penicillin in oil and wax have been as good as those with penicillin in aqueous solution. 4. Results of penicillin therapy in early syphilis are influenced by the composition of the patient population. 5. Results of penicillin therapy are better than indicated by reported data, since reinfections have been included with "failures."

Two possible methods of enhancing the therapeutic activity of penicillin are discussed: 1. Altering time-dosage relationships to give increased blood and tissue concentrations. Experience has shown that relatively low concentrations suffice provided that the treatment period is sufficiently prolonged. Total doses of less than 2,400,000 units have given progressively higher failure rates, while increasing the dosage above this has not resulted in a decreased failure rate. 2. Administration of other spirocheticides with penicillin. Lower failure rates have been obtained with penicillin and arsenicals than with penicillin alone, but the incidence of serious reactions is increased. It is suggested that a combination of bacitracin and penicillin may increase the cure rate with "readily innocuous and readily administered therapeutic agents."

209. Reynolds, F. W.: Nationwide Results in Treatment of Early Syphilis with Penicillin, Am. J. Med. **5**:679-686 (Nov.) 1948.

Blackwood, Scott and Clark [210] report the cumulative percentage of failures following the treatment of 123 patients with early syphilis by a schedule using 4,800,000 units of commercial sodium penicillin over a seven and one-half day period. Their figure of 16.7 per cent failures at the end of eleven months does not differ significantly from the results previously reported with 1,200,000 or 2,400,000 units. Because of the implications that the character of commercial penicillin has changed, the authors compared results by date of treatment; they found no significant differences between their results obtained with 4,800,000 units between August 1945 and February 1946, and those obtained with 1,200,000 units either before May 1944 or from November 1944 to February 1946.

Arnold, Mahoney and Nicholson [211] briefly review the order of events in successful penicillin therapy of syphilis. On the basis of an assumption that the optimal duration of early syphilis in man lies between one and eight days, the authors adopted a three day treatment schedule for a clinical trial. The purpose was to determine a cure rate for three days of therapy. The three day schedule consisted of intramuscular injections of 200,000 units of aqueous penicillin every two hours for a total of thirty-six injections, making a total dose of 7,200,000 units in seventy-two hours. By fixing the dose at 200,000 units, the dosage factor was eliminated from the time-dose relationship. It is well known that 200,000 units is far in excess of the optimal dose; hence any treatment failure would be due to a time factor. Comparison of the retreatment rate for patients who had received 40,000 units of aqueous penicillin every two hours for eighty-five injections shows an approximate cumulative rate of 5 per cent for each group, which, of course, does not exclude patients who may have been reinfected. The three day schedule reduces the hospitalization period, and the time factor may be a basis of an ambulatory schedule. Studies show that 40,000 units given every two hours produces a serum level of 0.015 units per cubic centimeter. Procaine penicillin (300,000 units) incorporated in 2 per cent aluminum monostearate produces a serum level of 0.0125 unit per cubic centimeter for a period of three days. As a result of these studies two schedules for ambulatory treatment have been instituted. One schedule employs 600,000 units of procaine penicillin in aluminum monostearate given daily for three days. The second schedule employs 300,000 units

210. Blackwood, J. Q.; Scott, V., and Clark, E. G.: Treatment of Early Syphilis with Sodium Penicillin: A Preliminary Report with a Comparison of Results with 4,800,000 Units Administered in Seven and One-Half Days, with Smaller Dosages, Arch. Dermat. & Syph. **57**:1028-1041 (June) 1948.

211. Arnold, R. C.; Mahoney, J. F.; Nicholson, T. P., and Wright, R. D.: Penicillin Therapy in Early Syphilis: IV., J. Ven. Dis. Inform. **30**:125-127 (May) 1949.

of slowly absorbed penicillin. The favorable clinical and serologic response in the three day therapy may be a key to the solution of time factors in the ambulatory management of syphilis.

The accompanying table, prepared by Heyman,[212] presents all the pertinent data from his study of treatment on an ambulatory basis.

Chargin and his associates[213] report their observations with from eight to fourteen months' follow-up of 153 patients with early syphilis who were treated while ambulatory by a sixteen day schedule employing 4,800,000 units of penicillin in oil and wax (300,000 units daily). In comparison with shorter schedules, the presented methods seems to be more satisfactory in all categories. However, lengthening the schedule elevates the number of patients who fail to complete the course of treatment.

Cohn, Rosenthal and Grunstein[214] reported on 96 patients who were treated for early syphilis with penicillin in water-in-oil emulsion on an

Results of Treatment with Penicillin in Oil and Wax (9,600,000 Units)

	Total Number of Patients	Treatment Failure	Seronegative Reaction	Seropositive Reaction
Primary Syphilis	14	3*	11	0
Secondary Syphilis	44	8*	30	6
Recurrent Syphilis	17	4	11	2
Total	75	15 (20%)	52 (69.3%)	8 (10.6%)

* At least 1 of these patients appeared to be reinfected.

ambulatory basis. The total dosage ranged from 2,000,000 to 5,000,000 units over a period of five to ten days. Various brands of penicillin were employed in several treatment schedules. Complete healing of the primary lesions was observed within an average period of 12.2 days (minimum 3 days to maximum of 37 days) and the secondary lesions within an average period of 17.8 days (minimum 3 days to maximum of 120 days). In a group of 66 patients followed up for a period of three to twenty-six months, 55 showed satisfactory clinical and serologic progress; 7 underwent infectious clinical relapse and 2 serologic relapse.

212. Heyman, A.: Treatment of Early Syphilis with Penicillin in Oil and Wax, Arch. Dermat. & Syph. **58**:34-40 (July) 1948.

213. Chargin, L.; Sobel, N.; Rein, C., and Rosenthal, T.: Treatment of Early Syphilis with Penicillin Injection in Oil and Wax U. S. P.: Report of One Hundred and Fifty-Three Cases, Arch. Dermat. & Syph. **59**:595-605 (June) 1949.

214. Cohn, A.; Rosenthal, T., and Grunstein, I.: Ambulatory Treatment of Early Syphilis: An Experimental Study with Report of Injection of Penicillin in Water-in-Oil Emulsion, Arch. Dermat. & Syph. **57**:900-906 (May) 1948.

There was no apparent correlation between the treatment schedule (duration of treatment, frequency of injection) and the occurrence of infectious or serologic relapse.

Penicillin and Fever Therapy.—Penicillin and fever therapy were used concomitantly in 20 patients with early syphilis by Schwemlein and his co-workers.[215] They were divided into 2 groups and were treated with the same total amount of penicillin (1,200,000 units), administered over periods of seven and one-half days and thirty hours, respectively. On schedule A, 109 patients received 20,000 units of sodium penicillin intramuscularly every three hours for sixty doses over seven and one-half days, plus three three hour sessions of artificial fever at 106 F. (rectal temperature) on alternate days, beginning twenty-three hours after use of penicillin was started. Patients with positive, significant serologic titers after twelve months of observation were grouped as failures. On schedule B, 188 patients received 50,000 units of sodium penicillin intramuscularly every two hours for twelve doses, beginning a day prior to fever (600,000 units total). The patients were then placed in the hypertherm and given six hours of fever at 106 F., receiving 100,000 units of penicillin intramuscularly at each hour of elevated temperature (600,000 units total). This provided a total dose of 1,200,000 units of penicillin and six hours of fever in approximately thirty hours. The cumulative failure rate on schedule A was 17.9 per cent, as compared with a cumulative failure rate of 40.1 per cent on schedule B. According to the results of this study, fever therapy and penicillin administered over a seven and one-half day period proved to be more effective than the thirty hour method.

Fever Chemotherapy in Early Syphilis.—Rodriquez and his group [216] studied treatment of primary and secondary syphilis with fever combined with oxophenarsine hydrochloride and bismuth, fever and penicillin and combined fever, oxophenarsine hydrochloride, bismuth and penicillin. In the first group 630 patients were treated with fever in combination with oxophenarsine hydrochloride and bismuth. Each patient who completed the fever-chemotherapy schedule received various total doses of oxophenarsine hydrochloride: 60, 90 and 120 mg. One group received 1.76 mg. per kilogram of body weight. This was combined with a single intramuscular dose of 150 mg. of elemental bismuth given twenty-four hours prior to the day of fever therapy. Each patient received eight hours of fever maintained at 106 F. in a Kettering hyper-

215. Schwemlein, G. X.; Bauer, T. J.; Craig, R. M., and Rodriquez, J.: Penicillin and Fever Therapy in Early Syphilis, J. A. M. A. **137**:1209-1212, 1948.

216. Rodriquez, J.; Schwemlein, G. X.; Bauer, T. J.; Plotke, F.; Peters, E. E.; Kendell, H. W., and Rodriquez, A. A.: Fever-Chemotherapy in Early Syphilis, J. Ven. Dis. Inform. **30**:69-85 (March) 1949.

therm. The total dose of oxophenarsine hydrochloride was given in three equal parts. The first was given when the patient's temperature reached 106 F. and the second and third doses at the third and fifth hours of fever. The second group consisted of 131 patients treated with 100,000 units of penicillin every two hours for twelve doses. After this the patient received six hours of fever (106 F.) in a hypertherm, during which time he was given 200,000 units of penicillin hourly for 6 doses. The combined total dose of 2,400,000 units of penicillin and six hours of fever were all given within a period of thirty hours. The third group received a combination of fever oxophenarsine hydrochloride, bismuth and penicillin. One hundred and forty-one patients started therapy; only 137 patients completed the treatment. Each patient received 100,000 units of penicillin every two hours for twelve injections and then six hours of fever (106 F.), during which time the rest of the 2,400,000 units of penicillin was administered in hourly doses of 200,000 units. During fever the patient also received 1.76 mg. of oxophenarsine hydrochloride per kilogram intravenously in three equal doses at the first, third and fifth hours of fever. Bismuth subsalicylate in oil (2 cc.) was administered intramuscularly eighteen hours before fever. The authors are of the firm opinion that the combination of fever, oxophenarsine hydrochloride, bismuth and penicillin gives superior results, the cumulative failure rate for a fifteen month period being 13 per cent in a group of 137 patients. No serious reactions were observed. This study seems to present clinical evidence that early infectious syphilis can be effectively treated in thirty hours; no other form of treatment has given such high curative rates.

Penicillin and Chemotherapy.—McElligott, Jefferiss and Willcox [217] treated 275 patients, 151 with primary and 124 with secondary syphilis, with penicillin, neoarsphenamine, and bismuth for from six to ten weeks, the dosage of penicillin varying from 2,400,000 to 4,000,000 units given over a period of seven and one-half to twelve and one-half days. Two thirds of the male patients and half of the female patients were treated as outpatients with daily injections of penicillin in oil and wax. The rest were admitted to the hospital and given aqueous penicillin in a dosage of 40,000 to 75,000 units every three to four hours, the great majority receiving 50,000 units every four hours. A greater number of failures was noted in the smaller number of patients receiving aqueous penicillin. Toxic effects following the injections of the arsenicals were not negligible, and in 10 patients they were severe. Fifty-four per cent of the patients were followed for twelve to eighteen months or more; 70.2 per

217. McElligott, G. L. M.; Jefferiss, F. J. G., and Willcox, R. R.: The Treatment of Early Syphilis with Penicillin, Neoarsphenamine, and Bismuth, Brit. J. Ven. Dis. **24**:45-49 (June) 1948.

cent, for nine months or more, and 78.1 per cent for six months or more. Eleven failures were noted; 4 of the patients had recent genital lesions, and all had positive serum reactions. Critical examination might decrease rather than increase this number in the light of the possibility of reinfection in 4 cases. The failure rate is probably in the region of 4 to 7 per cent at twelve months, which compares favorably with that of 15 per cent at the same period for patients treated with penicillin alone. It is believed that prolongation of the total treatment time has lowered the incidence of infectious relapse and in some cases perhaps prevented further reinfection from regular consorts ("ping-pong syphilis"). The authors also feel that it is possible that the treatment time is of such a length as to impress the patient with the importance of an adequate follow-up but not long enough to weary him into default. It remains to be seen whether these good results can be achieved without resort to the toxic arsenicals and whether penicillin combined with bismuth, or even penicillin alone given over a longer period, will prove to be adequate in treatment of early syphilis.

Gustafson and Bowen [218] studied the quantitative serologic titer trends in 117 patients who were treated for seropositive early syphilis with commercial penicillin sodium. The patients were selected from a group of more than 700, the only criterion being a continuous and regular monthly determination of the serologic reaction of the blood for twelve months or longer. Of the series, 71 patients became seronegative and clinically well by the end of one year; 46 patients had either a serologic or a seroclinical relapse.

A case of early syphilis in a 22 year old Negro patient with hemophilia successfully treated with oral doses of penicillin was reported by Buerk and Tucker.[219] The data confirm the reports in the literature that effective plasma penicillin levels may be obtained by the oral use of penicillin, but approximately five times the intramuscular dose is necessary.

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218. Gustafson, M. H., and Bowen, J. H.: Quantitative Serologic Titer in Post-Treatment Observation of Early Syphilis Treated with Penicillin, Arch. Dermat. & Syph. **59**:303-307 (March) 1949.

219. Buerk, M. S., and Tucker, H. A.: Penicillin in the Treatment of Early Syphilis Complicating Hemophilia: Report of a Case Treated with Forty-Eight Million Units of Oral Penicillin G, Bull. Johns Hopkins Hosp. **84**:24-26 (Jan.) 1949.

(To Be Concluded)

News and Comment

GENERAL NEWS

Exhibition of American Physicians Art Association.—In conjunction with the meeting of the American Medical Association in San Francisco, June 26 to 30, the American Physicians Art Association will hold its twelfth art exhibition. By becoming a member, any physician may exhibit at this convention. Entry blanks and shipping labels may be obtained from the secretary, F. H. Redewill, M.D., 526 Flood Building, San Francisco 2, Calif.

Annual Meeting of American Association of Blood Banks.—The third annual meeting of the American Association of Blood Banks is being planned for Oct. 12, 13 and 14 at the Stevens Hotel in Chicago. The program will be of interest to all persons concerned in the procurement, preservation and administration of blood and blood derivatives. Further information may be secured from the Office of the Secretary, 3301 Junius Street, Dallas 1, Texas.

Book Reviews

How to Become a Doctor. By George R. Moon. Price, $2. Pp. 131. The Blakiston Company, 1012 Walnut St., Philadelphia 5, 1949.

This handbook will serve a useful purpose in acquainting the prospective medical student with the basic requirements of, and the mechanics of, securing admission to a medical school. It also presents a brief prospectus of the usual medical school course and a helpful discussion of personal problems such as finances, outside employment, marriage and health as they relate to the medical student.

Mr. Moon has adroitly evaded the problem of how to evaluate the various schools of medicine. He describes the first two years as being so highly standardized that it makes no difference where the student begins his training. He comments on the lack of standardization in the last two years but refers to the uniformly good results achieved by graduates of all approved schools on examinations for medical licensure as indicative of uniformly good training. This judgment may serve the needs of diplomacy but does not serve those of the student seeking help in the selection of a school. It fails to indicate the tremendous difference between the best schools and the poorest, and it does not hint at the handicaps that may face the graduate of a poor school seeking specialized or graduate training.

The author's experience as a registrar undoubtedly gives him ample justification for including a section which urges the applicant to be neat and accurate in filling out the application forms, to include a transcript and a picture if requested and, finally, to avoid using mimeographed letters in support of the application. It is a wry commentary on our educational system that such elementary details need to be spelled out in bold print.

The related professions of dentistry, pharmacy, veterinary medicine and other allied sciences are discussed in a similar fashion, but with considerably less detail. One must admire Mr. Moon's courage in dealing with requirements for admission to an osteopathic college in the same volume that deals with admission to a school of medicine.

An Introduction to Gastro-Enterology. By Walter C. Alvarez, M.D. Fourth edition, revised and enlarged. Price, $12.50. Pp. 903, with 269 illustrations. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1948.

This book is the fourth edition of "The Mechanics of the Digestive Tract." The first edition appeared in 1922, and subsequent editions were published in 1928 and 1940. The present edition is considerably enlarged and gives additional information as to the effects of vagotomy in man. Also included are additional abstracts of 400 articles and books, increasing the bibliography to about 2,800 titles.

As in the previous editions, the author records his personal observations and deductions on the physiologic activity of the gastrointestinal tract. His ideas of intestinal rhythm are provocative. He explains such phenomena as hunger contractions, ulcer pains, flatulence, reverse peristalsis, heartburn, belching and vomiting on a gradient theory. He believes in a polarization of the bowel, a metabolic gradient and other related gradients of the bowel. It is stated that the discussions are largely theoretic, particularly when applied toward the explanation of gastrointestinal symptoms.

Many physiologists and gastroenterologists will disagree with the author's ideas and conclusions; nevertheless, this is a book which should be read because the ideas and interpretations presented are stimulating and provocative, though frequently highly theoretic. For students of gastrointestinal physiology, the bibliography is excellent and extensive.

In summary, this is not a book to be recommended unless the reader has an adequate and sound background and is able to formulate his own opinions and evaluations of many of the author's controversial deductions and explanations as they are related to gastrointestinal symptomatology and therapy.

An Atlas of Bone-Marrow Pathology. By M. C. G. Israels, M.D. Price, $6.50. Pp. 79, with 12 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This small monograph tells its story in a frank and engaging manner. The text is short and simply written, so that it is readily understandable. The bulk of the book is made up of diagrams and drawings—many of which are in color—so that any reader gets an attractive view of current hematology as seen through the eyes of a modern British hematologist.

As the preface states, the volume attempts to provide an authoritative, accurately illustrated account of the bone marrow in health and disease for the guidance of physicians and pathologists. It is modeled in a small-sized way on the atlas of the blood diseases of children that Blackfan and Diamond prepared in 1944. It should prove a useful handbook for students and for hospital or medical school libraries.

An Integrated Practice of Medicine: A Complete General Practice of Medicine from Differential Diagnosis by Presenting Symptoms to Specific Management of the Patient. By Harold Thomas Hyman, M.D. Volumes I, II, III and IV, and index. Price, $50 per set. Pp. 4,131, with 1,184 illustrations, 305 in color. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; Shaftesbury Ave., London W.C.2, 1947.

Here is a system of medicine in four volumes, comprising 4,131 pages and representing well over a million words of writing. It covers the entire field, medicine, surgery, obstetrics and all the specialties, and is unique in that it is edited and largely written by a single author.

To review a work of such character and dimensions is difficult. *Time* (77 [Feb. 10] 1947) gave it a two column notice, calling it "The Compleat Practitioner" and saying that it provides the family physician with a meticulously illustrated guide for the diagnosis and treatment of almost every human ill. This is not a bad description.

A study of several different chapters, selected haphazardly for reading, gives the impression that the information presented is sound and up to date. The literary style is clear and readable, the illustrations vary in quality, some being excellent, others fair and certain ones inferior, and the indexing is especially ingenious, so that one can lay one's hands on anything one chooses, from a description of the anatomy of the abdominal cavity to a definition of zygospore, without difficulty or loss of time.

Any writer with the patience, energy and imagination to compile so complicated a structure deserves high praise. The result of Dr. Hyman's labors is so gratifying that copies of his system of medicine are likely to appear in medical libraries and on physicians' bookshelves in increasing numbers. Indeed, "An Integrated Practice of Medicine" will never find itself out of place beside such distinguished predecessors as Allbutt, Nothnagel and Osler.

Intracranial Tumors. By Percival Bailey, M.D. Second edition. Price, $10.50. Pp. 478. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1948.

The appearance of a second edition of this book in a relatively short time after the first edition was published indicates that the book has been exceptionally well received. The favorable reception is well merited.

The text of this edition has few changes as compared to the text of the first edition. In fact, except for the addition of two plates in the beginning of the book and two or three new figures, the two editions are identical. The newer figures that are added bring the text more up to date. Several of the chapters could be enlarged by the addition of neurophysiologic and neuropathologic information that has appeared in the current literature. However, the contents of this book are for the student, and, therefore, added controversial data might lead to the confusion of such a reader. The book is impressive in its simplicity of form and its easy style. It gives the student a comprehensive, matter-of-fact survey of intracranial tumors. The text serves as an excellent guide and stimulus toward the pursuit of newer concepts in the pathology, neurophysiology and anatomy associated with intracranial tumors.

This later edition promises to maintain for the book the prominent position which it attained in the first printing. One can safely predict continued success for it.

Microbiology and Pathology. By Charles F. Carter, M.D. Price, $5. Pp. 845. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1948.

This textbook is designed for the use of student nurses in their course in microbiology and pathology. It contains sections on the general principles of microbiology, the relation of bacteria to disease, the bacteriology of water and milk, special bacteriology including the viruses, rickettsias, fungi and protozoa and both general and systematic pathology. There is also a section devoted to laboratory exercises, a glossary and a subject index.

The book contains information which is out of date, inaccurate and misleading. One example will suffice (page 393): "Acquired syphilis is most often contracted by direct contact, usually through sexual intercourse. The infection may be transmitted by kissing. . . . It is occasionally spread by contaminated objects such as drinking cups, towels, etc. Physicians and nurses may become infected while examining a syphilitic patient. Blood and semen may sometimes contain the organism." Are the nurses so sheltered that they no longer are to be taught such basic facts as the commonest site of a chancre? In view of such misleading statements, this reviewer cannot recommend the book for use in schools of nursing or elsewhere.

The Renal Origin of Hypertension. By Harry Goldblatt, M.D., C.M. Price, $2.75. Pp. 128, with 388 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1948.

This is a worth while monograph. One of its best features is the complete summarization of the work done by the author. It gives him an opportunity to correct impressions made by inaccurate quotations which have been frequent. There is also a thorough survey of other work done in this field particularly by the Argentine workers and by Page and his collaborators. Unfortunately, a bibliography is not included, and reference must be made to a similar article in *Physiological Reviews*. Since this publication is chiefly a review of the field, it would seem wiser to have included the complete bibliography in the bound copy.

The monograph is written with some bias which might be misleading. There is a fairly continuous defense of the theory which states that hypertensive vascular

disease is renal in origin. Such an approach is justified only when full statement of opposing evidence is included; this has not always been done. It must be understood by the reader not too familiar with the literature in this field that a much stronger compilation of evidence opposing the renal origin theory is available than the one given in the publication here reviewed.

Dr. Goldblatt's contributions have been of fundamental importance and have been amply confirmed. It is well for anyone interested in this field to be thoroughly acquainted with them. The point of departure has always been and remains the extent to which his data can be made to apply to the disease hypertension in man. More work must be done before this important question can be definitely answered.

Pathologie des Kohlehydratstoffwechsels. By Prof. Dr. E. Frank. Price, 24 Swiss francs. Pp. 342, with 17 illustrations and 3 graphs. Basel: Benno Schwabe & Company, 1949 (imported by Grune & Stratton, Inc., New York).

In this compact format, the author has provided a comprehensive review of current knowledge about diabetes mellitus and related disturbances of metabolism. Formerly an associate of Minkowski (who earlier had discovered pancreatic diabetes) in Breslau, and in recent years, director of the II Medical Clinic of the University of Istanbul, Professor Frank is eminently qualified for this task. He brings to it a wealth of personal experience, together with critical judgment. He has the rare ability to put first things first. He has a gift for lucid exposition, and his clear and vivid writing makes this German text easy reading for any one at all familiar with the subject matter.

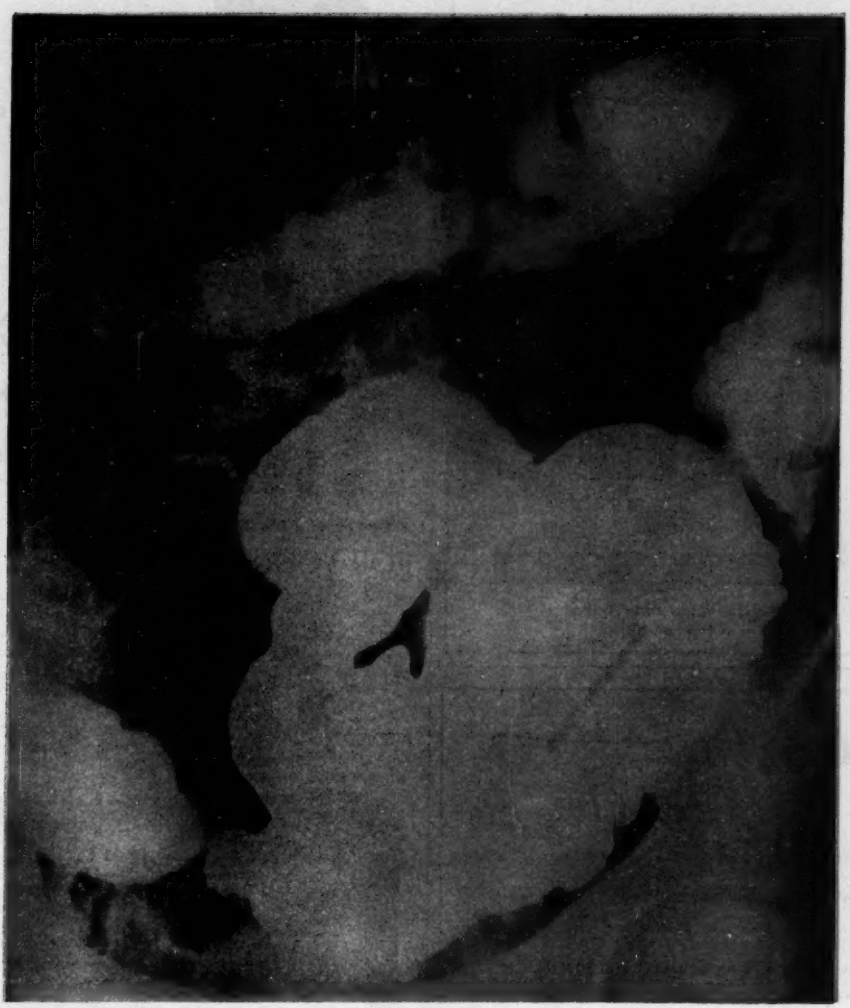
Clinical investigation joined hands with the more basic sciences of biochemistry, pathology and physiology in contributing to our present understanding of disorders of metabolism. Especially is this true of diabetic coma and of the several forms of spontaneous hypoglycemia, subjects which are given special emphasis. The chapter devoted to renal glycosuria, based as it is on the author's own investigations, represent a personal contribution to that subject.

The book is fully up-to-date. Very recent developments are treated in a number of addenda. One of them relates to experience with total extirpation of the pancreas in man, another to the significance of potassium in recovery from diabetic acidosis, another to the development of the newest forms of insulin containing crystalline protamine insulin.

The reader, as these pages are perused, has a sense of being in the hands of a most helpful guide, who leads him through the better known to the less familiar corners of the regions in which medical practice and the biologic sciences have become one discipline.

Rapid Microchemical Methods for Blood and C. S. F. Examinations. By F. Rappaport. Price, $8.75. Pp. 404, with 72 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This book contains information on up-to-date microchemical methods for the analysis of blood and spinal fluid. The essential contribution is the simplification of the laboratory procedures by decreasing the amount of material needed for analysis and by avoiding the use of expensive equipment. Such measures were fostered by wartime experiences with scarcity of materials and equipment; photometers and photoelectric colorimeters are only mentioned. The author has made a special point of giving detailed descriptions of all technical procedures and calculations. For this reason the book will serve as a valuable laboratory guide for workers inexperienced in microtechnics. Sufficient figures and tables are given to supplement the points made in the text. The bibliographies at the end of each chapter are most helpful.



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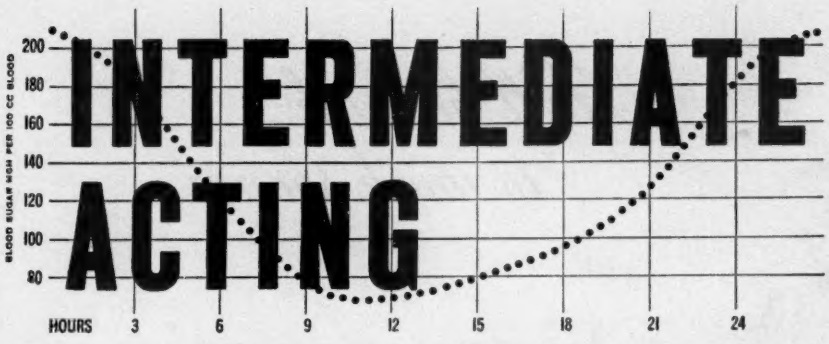

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
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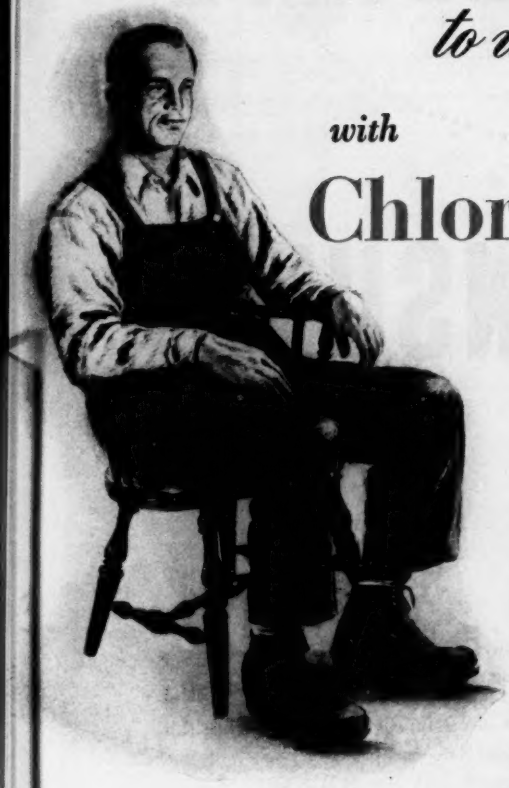

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